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# Upper Body Venous Compliance Exceeds Lower Body Venous Compliance in Humans

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National Aeronautics and  
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## Nomenclature

BP	blood pressure	$P_c$	capillary pressure
C	compliance	$P_v$	venous pressure
CVP	central venous pressure	SD	standard deviation
$G_z$	gravitational or similar acceleration stimulus directed parallel to body long axis	SE	standard error
HDT	head-down tilt	SLS	Spacelab Life Sciences
HIL	hydrostatic indifference level	SMCVP	system for measuring central venous pressure
HUT	head-up tilt	SVOP	system for venous occlusion plethysmography
$P_a$	arterial pressure	VP	venous pressure



# Upper Body Venous Compliance Exceeds Lower Body Venous Compliance in Humans

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## Summary

Human venous compliance hypothetically decreases from upper to lower body as a mechanism for maintenance of the hydrostatic indifference level "headward" in the body, near the heart. This maintains cardiac filling pressure, and thus cardiac output and cerebral perfusion, during orthostasis.

This project entailed four steps. First, acute whole-body tilting was employed to alter human calf and neck venous volumes. Subjects were tilted on a tilt table equipped with a footplate as follows: 90°, 53°, 30°, 12°, 0°, -6°, -12°, -6°, 0°, 12°, 30°, 53°, and 90°. Tilt angles were held for 30 sec each, with 10 sec transitions between angles. Neck volume increased and calf volume decreased during head-down tilting, and the opposite occurred during head-up tilt. Second, I sought to cross-validate Katkov and Chestukhin's (1980) measurements of human leg and neck venous pressures during whole-body tilting, so that those data could be used with volume data from the present study to calculate calf and neck venous compliance ( $\text{compliance} = \Delta\text{volume}/\Delta\text{pressure}$ ). Direct measurements of venous pressures during postural changes and whole-body tilting confirmed that the local changes in venous pressures seen by Katkov and Chestukhin (1980) are valid. The present data also confirmed that gravitational changes in calf venous pressure substantially exceed those changes in upper body venous pressure. Third, the volume and pressure data above were used to find that human neck venous compliance exceeds calf venous compliance by a factor of 6, thereby upholding the primary hypothesis. Also, calf and neck venous compliance correlated significantly with each other ( $r^2 = 0.56$ ). Fourth, I wished to determine whether human calf muscle activation during head-up tilt reduces calf venous compliance. Findings from tilting and from supine assessments of relaxed calf venous compliance were similar, indicating that tilt-induced muscle activation is relatively unimportant.

Low calf venous compliance probably results from stiffer venous, skeletal muscle, and connective tissues, and better-developed local and central neural controls of venous distensibility. This research establishes that upper-

to-lower body reduction of venous compliance can explain headward positioning of the hydrostatic indifference level in humans.

## 1. Introduction

Physiologic systems of animals have adapted to Earth's gravity over millions of years. In general, gravitational adaptations of the cardiovascular system are more pronounced in terrestrial species with greater height, and thus greater gradients of blood pressure from head to feet (fig. 1-1; Watenpaugh and Hargens, 1995), or from feet to head, as is probably the case with animals such as bats and sloths, which spend substantial portions of their existence in head-down positions. Upright species such as dinosaurs (Lillywhite, 1991; Millard et al., 1992), tree-climbing snakes (Scholander et al., 1968; Seymour and Lillywhite, 1976; Lillywhite, 1987), giraffes (Hargens et al., 1987 and 1988; Seymour et al., 1993), and other tall animals have evolved sophisticated mechanisms to provide adequate blood flow to their brains while restricting blood flow and tissue swelling in gravity-dependent tissues. Because humans are usually upright and relatively tall, they too have developed extensive and sophisticated anatomical and regulatory mechanisms to maintain cerebral perfusion and prevent lower extremity edema in upright posture.

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### 1.1 Gravitational Pressures Stress Dependent Vascular Structures: Wolff's Law and Vascular Characteristics

Structural and contractile tissues respond, within physiologic limits, to increased (or decreased) levels of mechanical stress by increasing (or decreasing) their functional capability and/or mass (Wolff, 1892; Carter,

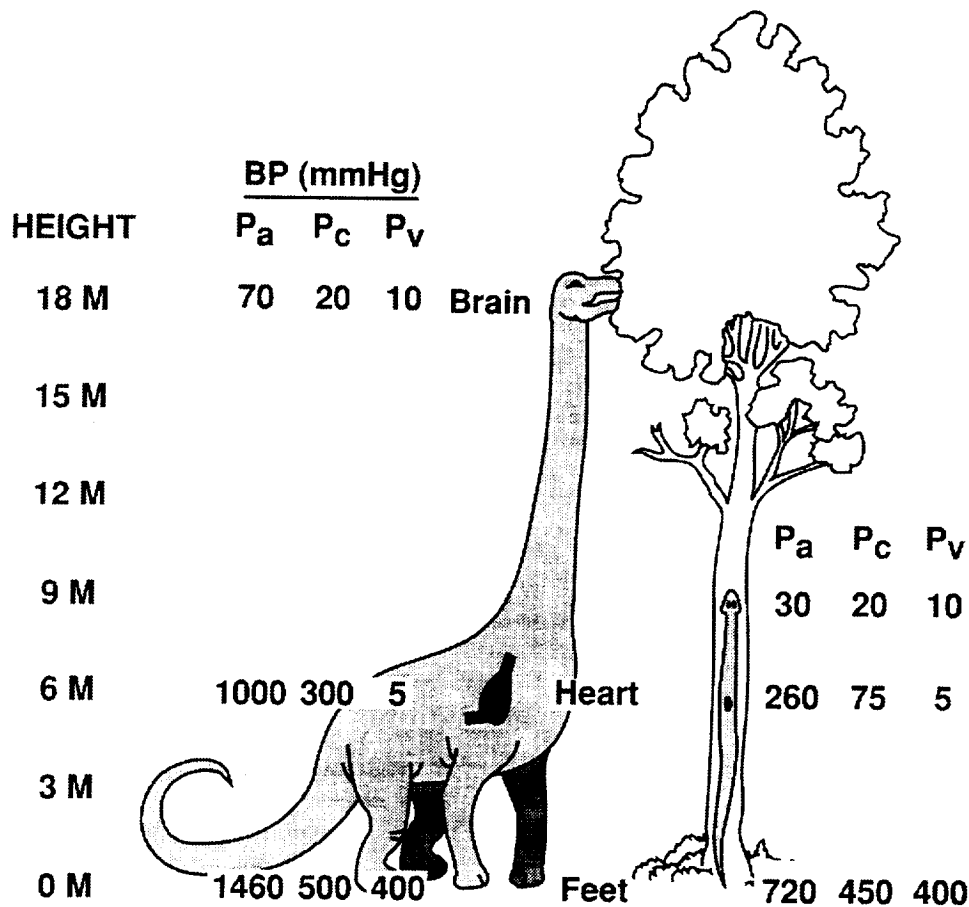


Figure 1-1. Blood pressure gradients hypothesized for a large terrestrial dinosaur and a tree-climbing snake ( $P_a$  = mean arterial pressure,  $P_c$  = capillary pressure,  $P_v$  = venous pressure; from Watenpaugh and Hargens, 1995).

1984; Lanyon, 1984; Hargens and Akeson, 1986; Yegorov, 1986). In the vasculature, such adjustments can begin within hours of initiation of the stress (Fung and Liu, 1991). Circulatory gravitational pressures impose mechanical stresses in smooth muscle and connective tissue of dependent vessels (Hargens et al., 1987 and 1988; Watenpaugh and Hargens, 1995). This stress stimulates these tissues to maintain their mass and structural integrity.

Measuring compliance of a structure provides one way to define and quantify its structural rigidity. Compliance is a mechanical property described by the deformation of the structure for a given level of applied stress. For a tissue or blood vessel, compliance equals a change in volume divided by the change in pressure required to elicit the volume change. Compliance of living tissues is determined primarily by the type and stiffness of the tissue, and to some extent by tissue hydration state (increased hydration reduces compliance). In the case of blood vessels, wall thickness, composition and smooth muscle content constitute primary determinants of

compliance. Compliance of tissues surrounding the vessels influences in situ vessel compliance, especially for relatively thin-walled veins, and neural input and vasoactive substances may also influence vessel compliance.

## 1.2 Regional Compliance Variation Hypothetically Sets the Hydrostatic Indifference Level

The research described herein will determine whether compliance of the upper body *venous* circulation is significantly greater than compliance of the lower body *venous* circulation in humans. Regional compliance variation provides the hypothetical mechanism for the "hydrostatic indifference level" concept. At any point in the circulation, the intravascular hydrostatic pressure ( $P_i$ ) produced by gravitational (or other) acceleration equals the product of: 1) the density of blood (approximately 1.06 g/ml); 2) the magnitude of acceleration; and 3) the distance of the point of interest above or below the hydrostatic indifference level (HIL), which is defined as that

place in the circulation where hydrostatic pressure remains constant with acute changes in orientation of the organism to the acceleration vector (Gauer and Thron, 1965; Blomqvist and Stone, 1983; Watenpaugh and Hargens, 1995). Thus,

$$P_i = \rho a h + \rho g h$$

where

- $a$  = nongravitational acceleration ( $\text{cm} \times \text{sec}^{-2}$ )
- $g$  = Earth gravitational acceleration constant =  $980.7 \text{ cm} \times \text{sec}^{-2}$
- $h$  = height of fluid column relative to the HIL (cm)
- $P_i$  = acceleration-induced intravascular hydrostatic pressure ( $\text{dynes} \times \text{cm}^{-2}$ , or  $\text{kg} \times \text{cm}^{-1} \times \text{sec}^{-2}$ , or mmHg)
- $\rho$  = density of blood ( $\text{gm} \times \text{l}^{-1}$ )

The variable  $h$  may be negative or positive, depending on whether the circulatory point of interest is above or below the HIL, respectively. The arterial and venous circulations can have different HILs. Clark and co-workers (1934) first introduced the HIL concept. They noted that upright human foot and dog hindlimb venous pressures were consistently less than would be predicted by the vertical distance from the heart, and they concluded that a non-cardiac reference point must exist in the venous circula-

tion where pressures do not change with orientation of the organism in gravity. They stated that the HIL "may be anywhere in the venous system, depending on the relative elasticity of its different parts." The HIL in the human venous circulation most commonly resides 5–8 cm below the diaphragm (Gauer and Thron, 1965).

The venous HIL determines cardiac filling (central venous) pressure during orthostasis, because filling pressure decreases according to the vertical distance between the heart and the HIL. HIL location depends on the relative vascular compliances in the circulation, such that the HIL moves away from regions of low compliance toward regions of high compliance (fig. 1-2). In humans, calf venous compliance should hypothetically be low to prevent excessive pooling of blood and reduction of cardiac filling pressure during orthostasis, yet little physiologic need exists for low venous compliance in the upper body. In fact, low venous compliance in the upper body would push the HIL footward during orthostasis, and thus counteract the headward HIL positioning imposed by low leg venous compliance. Therefore, if upper body venous compliance decreases, or if lower body venous compliance increases, the HIL would shift further below the heart. Such a shift compromises cardiac function during an orthostatic challenge, because cardiac filling pressure decreases to a greater extent than if the HIL is nearer the heart.

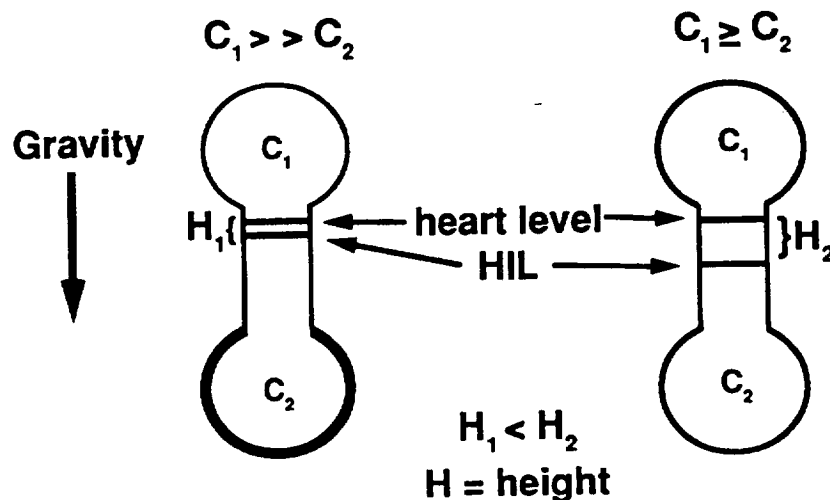


Figure 1-2. Illustration of how regional venous compliances ( $C_1$ : upper body, and  $C_2$ : lower body) affect cardiac filling pressure. Relatively stiff, noncompliant lower body tissues hypothetically "push" the HIL towards heart level, such that height  $H_1$  produces only moderate reduction of cardiac filling pressure when orthostatic. If chronic, microgravity-induced equilibration of regional vascular transmural pressures leads to relatively uniform regional compliances, the HIL shifts further away from the heart ( $H_2 > H_1$ ). Upon subsequent orthostasis in gravity, cardiac filling pressure would thus be compromised, because it decreases in proportion to the height between the HIL and heart (from Watenpaugh and Hargens, 1995).

### 1.3 Upper-to-Lower Body Macrovascular Compliance Reduction Has Not Been Established

What is known about upper versus lower body venous compliance differences in humans? At the tissue level, Kirsch et al. (1980b) demonstrated regional differences in cutaneous tissue compliance: they used a miniature plethysmograph (Kirsch et al., 1980a) to show that skin over the frontal bone, sternum (T3) or vertebral column (T9–11) was 1.5 to 3 times more compliant than skin over the tibia. Their 15 male subjects were tilted head-down 5°, which may have reduced forehead skin compliance by hyperhydrating those tissues (Parazynski et al., 1991). Regional differences in vascular compliance are not well studied. Two investigations have compared arm and leg venous compliances. Using conventional mercury strain gauge plethysmography, Journo et al. (1989) found calf venous compliance to be 40% greater than forearm venous compliance in 28 normal supine male subjects (calf:  $5.7 \pm 2.6 \text{ ml} \times \text{mmHg}^{-1} \times 10^2$ ; forearm:  $4.1 \pm 1.4 \text{ ml} \times \text{mmHg}^{-1} \times 10^2$ ; mean  $\pm$  SD). Gamble et al. (1992) found a similar, albeit statistically insignificant, trend using similar methods in eight subjects. Therefore, results of Journo et al. (1989) and Gamble et al. (1992) seem to refute the hypothesis that upper body venous compliance exceeds lower body compliance. However, the forearm is a questionable site for testing this hypothesis because, like the leg, the forearm is usually *below* heart level during normal daily activity. Because the forearm is a “dependent” circulation, and is not chronically weight-bearing like the leg, the forearm might be expected to exhibit less venous compliance than the leg to prevent blood and fluid accumulation in the forearm. This possibility seems still more reasonable in light of the biomechanical disadvantage organisms experience by adding weight to distal limb segments (Bligh, 1976).

### 1.4 Use of the Neck to Assess Upper Body Venous Compliance

The neck is a better site than the forearm for assessing upper body compliance in comparison to the leg in humans. Like the forearm, the neck has a similar tissue composition to the calf (largely skin and muscle), and therefore minimizes potential compliance differences due simply to differences in tissue type. (The trachea constitutes one exception to this generalization; however, this cartilaginous structure is basically noncompliant relative to skin and muscle, and therefore may be ignored for these purposes.) Most importantly, and in contrast to the forearm, the neck circulation resides almost constantly *above* heart level during normal daily activity. Thus, human neck veins are not chronically stressed by gravi-

tationally imposed pressures, as are veins in the forearm. The human neck vasculature is truly a nondependent circulation, and would not be expected to exhibit the same lack of compliance as expected in vessels chronically stressed by high gravitational pressures, such as those in the leg. Therefore, *I hypothesize that venous compliance of the calf is less than that of the neck in humans.*

The next four sections detail the process of testing this hypothesis. Section 2 describes the use of whole-body tilting to elicit the calf and neck venous volume changes necessary for calculation of local venous compliances. Section 3 validates use of the literature (Katkov and Chestukhin, 1980) for the calf and neck venous pressure changes necessary for calculation of local venous compliances. Section 4 is devoted to combining the local venous volume and pressure data for testing the primary hypothesis: does neck venous compliance exceed leg venous compliance? Section 5 describes a necessary supporting study to determine whether leg muscle activation during head-up tilt (HUT) significantly reduces leg venous compliance. Finally, section 6 summarizes the findings and presents some options for future related research.

## 2. Monitoring Acute Whole-Body Fluid Redistribution with Changes in Calf and Neck Volumes

This section describes the use of plethysmography to assess acute relative changes in fluid distribution during whole-body tilting. Metal-in-silastic strain gauge plethysmography has been used in the past to quantify percent changes in calf volume, yet the method has never been applied to assess upper body fluid redistribution simultaneously. Whole-body fluid volume redistribution is physiologically important because it contributes to cardiovascular acclimation to altered posture or gravity. For example, lower body vascular pressures decrease, and upper body and intracranial pressures increase in situations where fluids shift from the lower to upper body, such as supine posture, head-down tilt (HDT), and microgravity (Hargens et al., 1983; Thornton et al., 1987; Norsk et al., 1987; Parazynski et al., 1991; Murthy et al., 1992). Headward fluid redistribution stimulates low- and high-pressure baroreceptors, which in turn reduce sympathetic tone, systemic arterial blood pressure, vasopressin secretion, and renin-angiotensin-aldosterone activity, and increase urine production (Henry-Gauer reflex; Robertson, 1985; Bakris et al., 1986; Mark and Mancina, 1983). If recumbency or microgravity is prolonged for days to weeks, blood volume decreases, followed by reduction of orthostatic tolerance and upright exercise capacity (Blomqvist and Stone, 1983; Convertino et al., 1990). Because supine posture and HDT elicit these

responses by minimizing or counteracting cardiovascular effects of gravity seen in upright humans, investigators have hypothesized that a similar sequence of events occurs in the microgravity of space flight.

A convenient, sensitive, and noninvasive technique to quantify relative changes in fluid volume distribution is needed. In this study, we sought to determine whether changes in calf and neck volume provide sensitive indicators of acute fluid redistribution during tilting maneuvers in humans. I hypothesized that neck volume increases and calf volume decreases with acute tilt from vertical to horizontal and head-down positions, with the opposite occurring during subsequent return to HUT.

## 2.1 Methods

Nine subjects (4 females, 5 males) took part in these studies. They weighed  $64.7 \pm 12.6$  kg (mean  $\pm$  SD), were  $169 \pm 8$  cm tall, and were between 20 and 47 years old. Standing calf circumference (measured with a tape measure) averaged  $36.6 \pm 2.9$  cm, and neck circumference averaged  $34.6 \pm 4.5$  cm. The NASA Ames Human Research Institutional Review Board approved this research, and subjects gave informed consent to participate.

Strain gauge plethysmography measured changes in calf and neck volumes. Strain gauges consisted of silastic tubing filled with mercury (Whitney, 1953), or with a 4:1 gallium:indium alloy with a freezing point of approximately 16°C. Gauges were placed on the left calf at its maximal girth, and around the neck about 1 cm distal to the hyoid. Preliminary studies indicated that the legs respond similarly to one another. Strain gauges actually measure changes in circumference (to  $\pm 0.1$  mm or better); volume is calculated either manually or electronically by assuming that the calf and neck have circular cross sections, such that circumference =  $2\pi r$ . Cross-sectional area thus equals  $\pi r^2$ , and volume (to  $\pm 0.1$  ml or better) equals this amount multiplied by an arbitrary tissue slice thickness of 1 (Whitney, 1953). Therefore, volume may be expressed in absolute terms, or division of volume change by initial (baseline) volume yields percent change in volume.

Preliminary studies showed that minor leg or head movements could produce significant artifacts in volume measurement. In fact, some investigators use strain gauges instead of electromyography to monitor subject activity during experiments in which subjects are supposed to remain still, such as orthostatic tolerance tests (S. M. Fortney, personal communication). In this study, subjects remained relaxed and still throughout data collection. Broad foam cushions (5 cm thick) supported

the legs and head to ensure comfort, to help prevent any leg or neck movement during tilting, and to prevent contact between the strain gauges and the tilt table. Subjects were not allowed to talk or sleep during data collection.

Subjects underwent the following protocol on a motorized tilt table equipped with a footplate, where  $G_z$  equals the sine of the tilt angle: 90° (upright standing; 1.0  $G_z$ ), 54° (0.8  $G_z$ ), 30° (0.5  $G_z$ ), 12° (0.2  $G_z$ ), 0° (supine; 0.0  $G_z$ ), -6° (HDT; -0.1  $G_z$ ), -12° (-0.2  $G_z$ ), -6°, 0°, 12°, 30°, 54°, and back to the control position of 90°. In pilot studies, each tilt angle was held for 2 min, and we noted that 90% or more of the calf or neck volume change during the 2 min at a given tilt angle occurred within the first 30 sec, at which time volume signal began to level off. Multiple studies have shown that the relative contribution of capillary filtration (i.e., extravascular tissue volume elevation) to limb volume elevation increases with duration of an intravascular pressure increase (Schnizer et al., 1978; Vissing and Nielsen, 1988; Watenpaugh et al., in press). In other words, the longer a given tilt table angle is held, the less of the calf or neck volume change seen will be due to intravascular volume expansion. In order to study primarily *intravascular* events, we shortened the amount of time at each tilt angle to 30 sec, with 10 sec transitions between positions.

Data were digitized continuously at 2 Hz with a 286-based microcomputer equipped with data acquisition hardware (Metrabyte, Taunton, Massachusetts) and software (Labtech Notebook, Wilmington, Massachusetts). Data were averaged offline over the last 5 sec of each 30 sec position interval. Repeated measures ANOVA with post hoc paired t-tests identified statistically significant effects of tilt on calf and neck volume at  $\alpha = 0.05$ . Paired t-tests also identified hystereses. Linear regression/correlation analysis was performed on data during tilt from 90° to -12° to relate changes in calf and neck volumes (Zar, 1984). Data are presented as means  $\pm$  SE.

## 2.2 Results

Neck volume increased and calf volume decreased during tilting downward from vertical, and the opposite occurred when proceeding from HDT to vertical (fig. 2-1). Neck volume increased significantly from 90° baseline levels at all post-baseline tilt positions, including return to 90° upright position. Calf volume decreased from baseline at 30° HUT and below this level. For both the calf and neck, changes in volume between 0° horizontal and all other (head-up and head-down) tilt angles were also significant. Hysteresis between downward and upward tilt responses was observed in the calf and neck (fig. 2-2). For any given head-up or head-down tilt angle, increases in neck

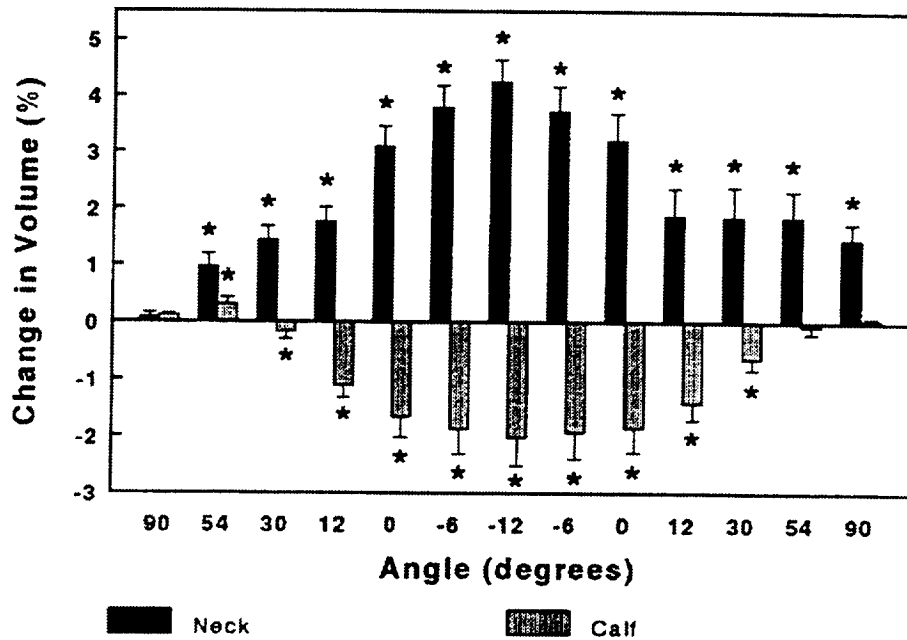


Figure 2-1. Percent changes in calf and neck volumes with tilt from head-up positions to head-down positions and back (means  $\pm$  SE). N = 9; \* Different from upright control (90°),  $P < 0.05$ . Mean values at 0° supine were significantly different from those at all other angles. Values at baseline were not different from 0.

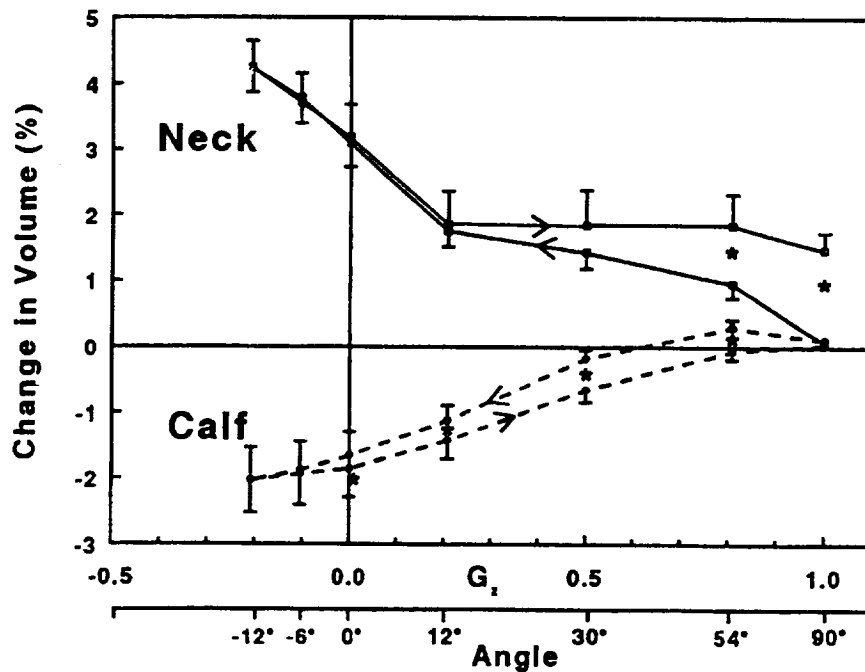


Figure 2-2. Calf and neck volume data (means  $\pm$  SE) plotted as hysteresis curves against effective  $G_z$  level produced by tilt ( $G_z = \sin(\text{tilt angle})$ ); \* significant hysteresis,  $p < 0.05$ .

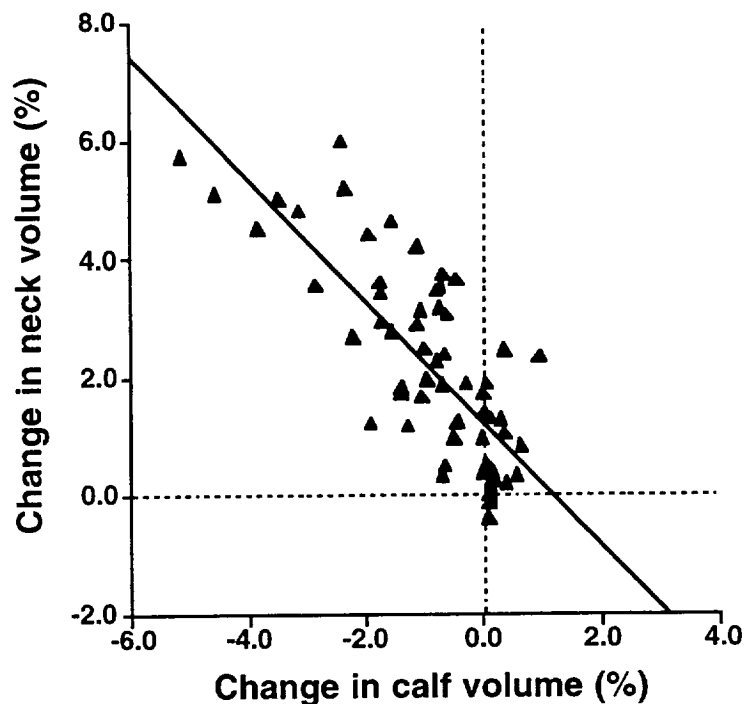


Figure 2-3. Regression of neck volume percent change against calf volume percent change using the downward tilt data ( $90^\circ$  through  $-12^\circ$ ) yielded the formula:  $\% \Delta \text{neck} = -0.98(\% \Delta \text{calf}) + 1.36$ ; 60 data points,  $r^2 = 0.60$ , SE slope = 0.11.

volume consistently exceeded the absolute magnitude of decreases in calf volume. For example, volume of the calf segment studied decreased  $1.66 \pm 0.36\%$  (1.8 ml) on average when going from vertical ( $90^\circ$ ) to horizontal ( $0^\circ$ ) position, while neck segment volume increased  $3.09 \pm 0.37\%$  (2.9 ml) between those positions. Change in neck volume correlated negatively with change in calf volume during tilting ( $\% \Delta \text{neck} = -0.98(\% \Delta \text{calf}) + 1.36$ ; 60 data points,  $r^2 = 0.60$ , SE slope = 0.11; fig. 2-3). Coefficients of variation for segment volumes in two subjects undergoing three repeated tilting procedures equaled 0.3% (0.003) or less.

### 2.3 Discussion

These results demonstrate that neck and calf volume changes provide sensitive indicators of tilt-induced fluid redistribution in humans. Because most of the volume changes occurred immediately upon changing tilt angle, intravascular redistribution of blood probably constitutes the majority of the response: venous blood moved into the neck with decreasing  $G_z$ , and into the legs with increasing  $G_z$ . The neck volume relationship with  $G_z$  was markedly biphasic, displaying increased sensitivity between  $12^\circ$  and  $-12^\circ$  of tilt (fig. 2-2). The hysteresis at the neck was probably due to residual venous distension from prior

HDT, while hysteresis in the calf was probably due to a somewhat slower time constant of venous filling relative to emptying. Due to the acute nature of this study, calf volume decreases seen during HDT were two- to five-fold less than those reported previously for longer-duration recumbency (Hargens et al., 1983; Convertino et al., 1989). This observation may be attributed to tissue fluid reabsorption from and muscle atrophy in the legs during the longer studies.

Correlation analysis suggests that 60% of the variation in neck volume seen in this study is explicable by changes in calf volume (fig. 2-3; Zar, 1984). Therefore, the amount of fluid leaving the legs during HDT in part determines the volume of fluid responsible for increasing neck volume. The slope of the neck/calf volume relationship indicates that over the full range of tilt, neck volume increases about 1% for each 1% decrease in calf volume. However, neck volume increased more than calf volume decreased at each tilt angle. This difference in apparent distensibility between the two sites is even more notable when considering that venous pressure (VP) in the calf must have increased substantially more going from  $-12^\circ$  to  $90^\circ$  (approximate increase of 80 mmHg) than did venous pressure in the neck when going from  $90^\circ$  to  $-12^\circ$  (approximate increase of 20 mmHg). This observation suggests that veins in the neck may be inherently more

compliant than those in the lower body, because the upper body circulation is not continually challenged with, and therefore not adapted to large gravitational pressure changes (Aratow et al., 1991; Hargens et al., 1992). Furthermore, major leg veins are deeply embedded in skeletal muscle (Buckey et al., 1988), and for that reason may display less compliance than veins in the neck. Also, the neck represents a much smaller total tissue volume than the legs.

Use of strain gauge plethysmography for the application described in this paper involves some assumptions (Whitney, 1953). First, calculations of volume change assume an approximately circular cross section of the tissue segment being measured (see 2.1). This assumption is justified for both the neck and calf (Siggaard-Anderson, 1970). Second, extrapolation of findings from the tissue segment measured to nearby tissues assumes that they behave similarly. Although the ratio of soft tissue to bone changes along the leg, this assumption is at least qualitatively reasonable for both calf and neck. Third, use of this method in the neck assumes that tracheal diameter remains constant. This assumption is also justified, because the cartilaginous trachea, like bone, is noncompliant relative to skin, muscle, and other “soft” tissues.

The advantages of using strain gauge plethysmography for this application outweigh the disadvantages. The principal disadvantages are: 1) susceptibility to motion artifact (including swallowing) and limb or head orientation; and 2) inability to distinguish easily between intra- and extravascular volume changes. Advantages include: 1) high sensitivity; 2) noninvasiveness; 3) remarkable repeatability (as evidenced by intraindividual coefficients of variation of 0.3% or less); and 4) convenience/ease of use. Other types of plethysmography (mechanical, pneumatic, hydraulic, impedance, ultrasonic) may work equally well or better in specific applications. Furthermore, changes in neck volume may correlate with changes in central venous pressure to provide a convenient, noninvasive index of central venous pressure (CVP) in a variety of experimental conditions, including space flight.

### 3. Summary and Confirmation of Human Venous Pressure Data from Literature

As presented in section 1, compliance of a blood vessel such as a vein equals a change in volume divided by the change in pressure required to elicit the volume change. Regional compliance variations (lower body venous compliance < upper body venous compliance) hypothetically position the hydrostatic indifference level near the heart, thus allowing maintenance of cardiac filling

pressure while upright. Section 2 described how whole-body tilting may be used to elicit quantitative calf and neck venous *volume* changes. Similarly, Katkov and Chestukhin (1980) have quantified venous *pressure* changes in neck and leg veins during whole-body tilting in a study they performed largely for that purpose. Therefore, calf and neck venous compliance may be calculated by dividing the volume changes described in section 2 by the venous pressure changes quantified by Katkov and Chestukhin (1980). However, such an approach clearly requires assurance that the venous pressure data reported by Katkov and Chestukhin (1980) are valid and reproducible. The purpose of this section 3 is to assess this validity. Some of my data presented in this section have appeared in another publication (Aratow et al., 1993b) or are submitted for publication (Buckey et al., in press; Buckey et al., in revision).

#### 3.1 Confirmation of Katkov and Chestukhin's Leg Venous Pressure Data Using Postural Change

Articles from the literature besides Katkov and Chestukhin (1980) agree with their data for leg venous pressure changes resulting from changes in posture or tilt in humans (see 3.3). I will present only one of those articles in detail (Aratow et al., 1993b; I was the co-author responsible for leg venous pressure measurements). Aratow and co-workers studied six healthy male subjects after they provided informed consent to participate (ages: 23–41 years; height:  $175.9 \pm 4.6$  cm; weight:  $74.2 \pm 7.8$  kg, mean  $\pm$  SD), and the protocol was approved by human research committees at the NASA Ames Research Center and Johnson Space Center. All data collection took place at Johnson Space Center, Houston, Texas. Katkov and Chestukhin (1980) studied 10 healthy male subjects (ages: 29–40 years; height:  $174 \pm 4$  cm; weight:  $71.3 \pm 4.3$  kg, mean  $\pm$  SD).

Aratow et al. (1993b) quantified the effects of lower body negative pressure on leg transvascular pressures and systemic transcapillary fluid transport. Part of the study involved measurement of supine and standing leg venous pressures prior to lower body negative pressure exposure. We measured leg venous pressure to  $\pm 0.5$  mmHg with a Gould Statham P23 pressure transducer attached via pressure tubing to an 18–22 gauge, 3 cm intravenous catheter. The catheter was placed in the great saphenous vein or one of its branches at the foot or ankle, similar to Katkov and Chestukhin (1980). To prevent clotting of the catheter, it was filled and flushed periodically with isotonic saline containing 30 units of heparin per ml. The pressure transducer was oriented vertically. The pressure transducer signal was recorded on an Astromed MT9500 chart recorder. Supine measurements were made first. To

avoid hydrostatic artifacts from the fluid-filled pressure measuring system, the transducer was leveled with the catheter tip before any readings were taken. Subjects then stood up, bearing equal weight on both feet for 10 min. The transducer was re-leveled with the catheter tip soon after standing, and leg venous pressure recordings continued.

**3.1.1 Results–** We found that leg venous pressure had equilibrated by the time the transducer was re-leveled with the catheter tip (usually about 1 min). The earliest standing data reported in Aratow et al. (1993b) were at 2 min because that was the longest it took to re-level the transducer. Venous pressure at foot level increased from supine values of  $6 \pm 1$  mmHg (mean  $\pm$  SE) to  $77 \pm 4$  mmHg at 2 min of standing. No significant additional increase in pressure occurred between 2 and 10 min of standing. Therefore, the acute (2 min) supine-to-standing change in foot-level venous pressure averaged 71 mmHg in these six subjects.

Katkov and Chestukhin (1980) reported supine foot venous pressures averaging 20.8 mmHg, which increased to 89.7 mmHg after 5 min at 75° HUT ( $n = 10$ ). Therefore, the acute change in foot-level venous pressure elicited by supine-to-75° HUT averaged 68.9 mmHg in their study, which is in good agreement with the 71 mmHg change seen by Aratow et al. (1993b). (See fig. 3-1.) However, 75° HUT corresponds to 0.97  $G_z$  ( $\sin[75] = 0.97$ ), yet standing = 90° HUT = 1.0  $G_z$ . To correct for this minor difference, 75° HUT values may be multiplied by the ratio  $\sin(90)/\sin(75)$ , yielding 90° HUT foot venous pressure of 92.5 mmHg. The supine-to-90° change calculated from Katkov and Chestukhin (1980) is thus 71.7 mmHg, which more closely approximates the 71 mmHg change reported by Aratow et al. (1993b). The age range and mean height and weight of the two subject groups were statistically similar (t-test,  $p > 0.2$ ).

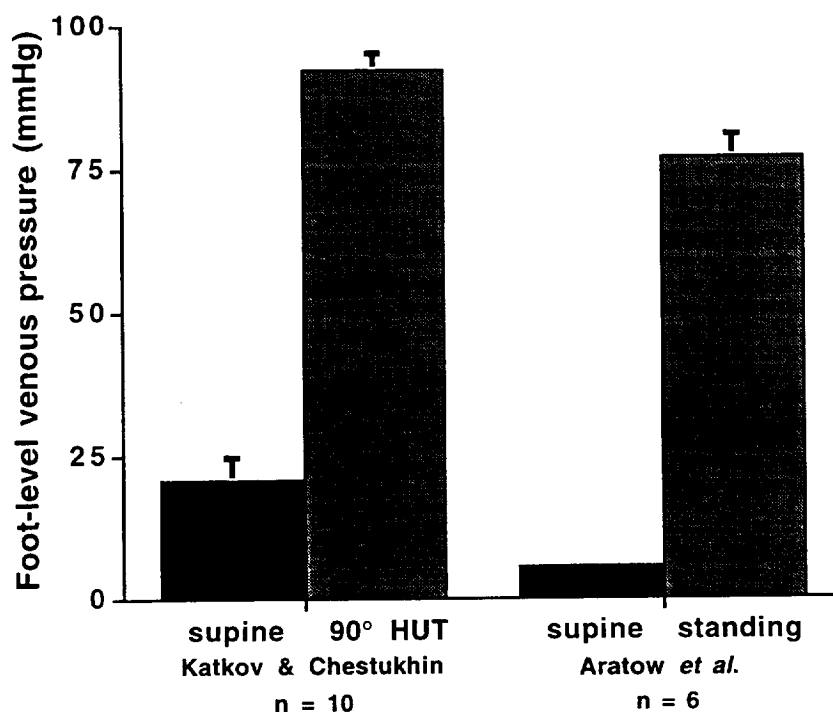


Figure 3-1. Supine and upright foot-level venous pressure found by Katkov and Chestukhin (1980; means  $\pm$  SD,  $n = 10$ ) and Aratow et al. (1993b; means  $\pm$  SE,  $n = 6$ ). Katkov and Chestukhin 90° HUT data were calculated by multiplying 75° HUT values by the ratio  $\sin(90)/\sin(75)$ . Supine-to-upright venous pressure elevation averaged 71–72 mmHg in each study.

Although the absolute values of pressure reported in each work differ, the supine-to-standing changes in foot venous pressure agree, and it is the *changes* in pressure which are important to calculation of compliance, because compliance equals the slope of the volume/pressure relationship. Differences between the two studies in absolute values of foot-level venous pressure probably result from differences in transducer leveling technique. Pressure measurements stabilize within several seconds of a change in posture or tilt angle if the subject remains still (see below; Pollack and Wood, 1949). Katkov and Chestukhin (1980) used 5 min of tilt because they were also measuring arterio-venous oxygen differences. They needed to allow time for the metabolic state of the perfused tissues to stabilize before they made measurements. Therefore, foot-level venous pressure results of Aratow et al. (1993b) support use of tilt data from Katkov and Chestukhin (1980) for calculation of regional venous compliances with the whole-body tilting protocol presented in section 2.

### 3.2 Confirmation of Katkov and Chestukhin's Leg Venous Pressure Data using Whole-Body Tilting

In addition to the confirmation provided by data from Aratow et al. (1993b) during posture change, we attempted to confirm Katkov and Chestukhin's (1980) leg venous pressure findings during whole-body tilting in two healthy male subjects after they gave informed consent. Our procedures were approved by the NASA Ames Human Research Institutional Review Board.

In the first subject, four attempts to catheterize large ankle veins failed for a variety of reasons. A small vein on the dorsolateral surface of the right foot was successfully catheterized with a 22 gauge (pediatric) catheter (per Aratow et al., 1993b; see 3.1). However, persistent bleed-back occurred into the catheter and extension tubing, and pressure data from this site exhibited anomalies due to foot loading and slow response time. A leak was suspected in the connections between the catheter, fluid-filled extension tubing, and pressure transducer, but we were unable to correct the problem, so the pressure data were not used.

The second subject (26 year old male, 182 cm tall, 86.6 kg) was successfully catheterized with a pressure transducer-tipped catheter (Millar Instruments, Inc.) in a large distal branch of the great saphenous vein at the ankle. The catheter's electronic calibration was confirmed with manual fluid-column calibration. Millar transducer-tipped catheters exhibit sensitivity to  $\pm 0.5$  mmHg or better. Venous catheterization entailed the following steps. Sterile technique was employed throughout the procedure. The subject reclined on a tilt table. A pressure

cuff was placed around the left thigh and inflated to sub-diastolic pressure to aid visualization of a vein suitable for catheterization. The chosen site of insertion was shaved and sterilized with a Betadine swab. An 18 gauge needle and surrounding Teflon sheath were inserted into the vein. The needle was withdrawn leaving the sheath in place. A 2F Millar catheter was then inserted into the vein through the sheath, and the sheath was withdrawn from around the catheter. An Op-Site (a wide, transparent, adhesive plastic dressing) was placed over the insertion site, and the remainder of the catheter was taped securely to the left leg.

Next, maximum girth of the calf of the catheterized leg was measured, and an Hg-in-silastic strain gauge (Hokansen, Inc.) was placed on the calf at the level of maximum girth (as in sec. 2). A wide strap around the upper abdomen gently secured the subject on the tilt table. We employed the following tilt table protocol, exactly as described in section 2 (Watenpaugh et al., 1993): 90° (HUT), 54°, 30°, 12°, 0° (horizontal supine), -6° (HDT), -12°, -6°, 0°, 12°, 30°, 54°, and 90°. Each position was held for 30 sec, and data were averaged over the last 5 sec of each interval. After short breaks (about 10 min), the tilt protocol was repeated twice to assess reproducibility of responses. Data were collected with an IBM-compatible computer data acquisition system. To determine venous pressures at the level of the calf strain gauge, data were corrected by subtracting  $G_z(h)$ , where  $G_z = \sin(\text{tilt angle})$ , and  $h$  was the distance between the catheter tip and strain gauge (10 cm in this case).

Katkov and Chestukhin (1980) employed head-up and head-down tilt angles of 10°, 30°, and 75°. Where we employed tilt angles different from those employed by Katkov and Chestukhin (1980), we linearly interpolated their venous pressure data according to the sine of the tilt angles ( $G_z$  levels) we employed. Also, we interpolated linearly between their femoral (groin level) and foot venous pressure measurements to derive venous pressures in the calf at the level of its maximum girth. In a typical subject, the level of maximum calf girth equals about 64% (0.64) of the distance from the femoral vein (groin level) to the foot.

As an example, the following calculations represent how I determined calf-level venous pressure at 54° HUT. All units are mmHg. First, I interpolated calf-level venous pressure from femoral- and foot-level venous pressures at both 30° and 75° HUT:

For 30° HUT, femoral VP = 11.1 and foot VP = 54.3:

$$\text{calf VP}_{30} = 11.1 + 0.64(54.3 - 11.1) = 38.8$$

For 75° HUT, femoral VP = 16.0 and foot VP = 89.7:

$$\text{calf VP}_{75} = 16.0 + 0.64(89.7 - 16.0) = 63.2$$

Second, I interpolated calf-level venous pressure at 54° HUT from the sines of 30°, 54°, and 75°, because gravitational pressures are proportional to the sine of the tilt angle (Gauer and Thron, 1965):

$$\begin{aligned}\text{calf VP}_{54} &= \text{calf VP}_{30} + (\text{calf VP}_{75} - \text{calf VP}_{30}) \\ &\quad \times \{[\sin(54) - \sin(30)] / [\sin(75) - \sin(30)]\} \\ &= 38.8 + (63.2 - 38.8) \\ &\quad \times \{[\sin(54) - \sin(30)] / [\sin(75) - \sin(30)]\} \\ &= 55.0\end{aligned}$$

Table 3-1 presents the results of these interpolations for all tilt angles employed. The only assumption involved in the above interpolations is that the physical laws of gravitational hydrostatics remain in force between the femoral and foot veins and at all tilt angles, which is reasonable.

Table 3-1. Calf venous pressure (VP) data from Katkov and Chestukhin (1980) during whole-body tilting, linearly interpolated as necessary to fit our experimental conditions\*

Tilt table angle (°)	G <sub>z</sub> (sin[tilt angle])	Calf VP (mmHg)
-12	-0.2	10.7
-6	-0.1	14.0
0	0.0	17.9
12	0.2	22.1
30	0.5	38.8
54	0.8	55.0
90	1.0	65.0

\*These interpolations assume that the physical laws of gravitational hydrostatics remain in force between the femoral and foot veins and at all tilt angles.

**3.2.1 Results**—Figure 3-2 presents data from our single subject and data from Katkov and Chestukhin (1980) plotted against the G<sub>z</sub> stimulation produced by our tilt protocol. At 30° HUT and above, our subject's venous pressures fall outside of one standard deviation from the means reported by Katkov and Chestukhin (1980). This is probably explained by subject height. Our subject was 182 cm tall (equal to their tallest subject), whereas their subjects averaged 174 cm in height. Nevertheless, our data are not outliers (they fall within two standard deviations of Katkov and Chestukhin's mean) and therefore further support use of their findings for calculation of calf

venous compliance. In three tilt trials with our subject, calf venous pressure coefficients of variation averaged 11%. However, coefficients of variation (SD/mean) become artificially high as means approach zero. For HUT angles ≥ 12° (calf venous pressures ≥ 30 mmHg), coefficients of variation averaged 0.9% in this subject, thus demonstrating remarkable reproducibility of venous pressure changes with tilt. Calf venous compliance was also highly reproducible in this subject, with a coefficient of variation of 2%.

### 3.3 Other Literature Supports Leg Venous Pressure Results of Katkov and Chestukhin

A comprehensive literature search retrieved many references reporting human venous pressure data during standing, postural change, or whole-body tilting. Pollack and Wood (1949) found a 75.1 mmHg supine-to-standing increase in ankle (saphenous) vein pressure in 11 subjects. They further noted that "the average time required for the venous pressure to increase to the standing value after the subject arose from the sitting to the standing position was 21.8 seconds." Hojensgard and Sturup (1953) measured ankle (saphenous) vein pressures averaging 76 mmHg in 12 standing subjects. Alimi et al. (1994) measured standing pressures of 39 mmHg in the popliteal vein just above the knee, and 75 mmHg in the saphenous vein just above the ankle (n = 9). Noddeland et al. (1983) noted saphenous vein pressures averaging 80 mmHg in eight standing subjects (178 ± 8 cm tall) with the catheter tip "about 20 cm above the sole of the foot." Grill (1937) found dorsal foot venous pressures averaging 94 mmHg in 12 standing subjects (174 ± 11 cm tall), which compares well with the 90° HUT foot venous pressure of 92.5 mmHg calculated from Katkov and Chestukhin (1980). Alexander (1972) measured standing saphenous vein pressure of 73 mmHg at ankle level in one subject. Keane and Fegan (1969) reported standing venous pressures of 83 mmHg in the lower calf (n = 12; exact catheter level unspecified). McIntire and Turner (1935) measured a 76 mmHg increase in foot venous pressure with 75° HUT from horizontal with an indirect technique in seven healthy young women, which compares well with the 68.9 mmHg increase seen by Katkov and Chestukhin (1980). McIntire and Turner (1935) also measured a 50 mmHg increase in foot venous pressure with 45° HUT from horizontal, which corresponds closely with the 52.9 mmHg increase interpolated from Katkov and Chestukhin (1980) 30° and 75° HUT data. Therefore, data from Aratow et al. (1993b), unpublished observations reported here, and the scientific literature collectively confirm the leg venous pressure findings of Katkov and Chestukhin (1980) and support use of those data for calculation of leg venous compliance.

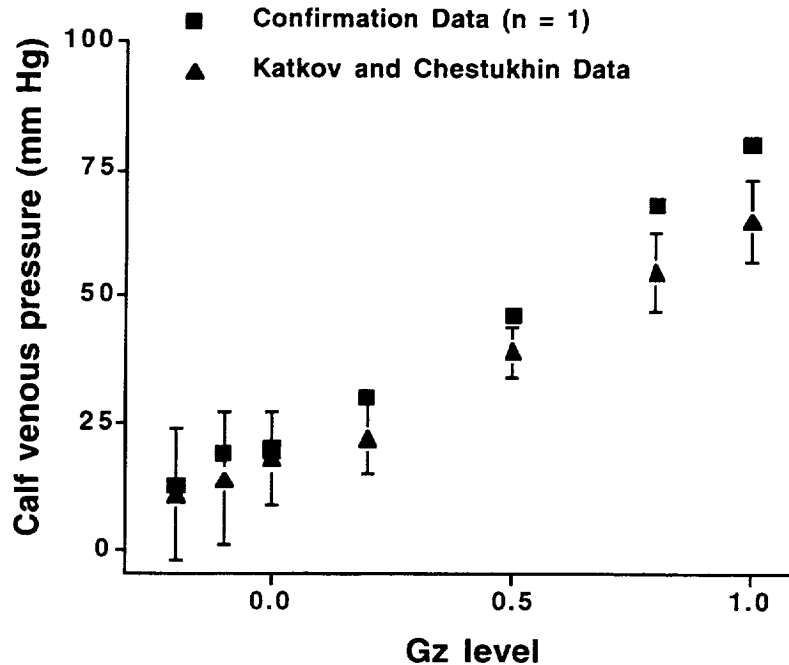


Figure 3-2. Calf venous pressures from our single subject (squares), and linearly interpolated data from Katkov and Chestukhin (1980; triangles = means  $\pm$  SD;  $n = 10$ ) plotted against the  $G_z$  stimulation produced by our HUT protocol ( $\sin[\text{tilt angle}] = G_z$ ).

### 3.4 Confirmation of Katkov and Chestukhin's Upper Body Venous Pressure Data using Postural Change and Whole-Body Tilting

Neck venous compliance may be calculated by dividing the volume changes described in section 2 by the jugular venous pressure changes quantified by Katkov and Chestukhin (1980). To validate Katkov and Chestukhin's 1980 findings in an upper body site, CVP data collected during postural change and HDT were used. These data were collected as part of the Spacelab Life Sciences (SLS) series of Shuttle flights during pre-flight baseline conditions. Part of the protocol involved measurement of CVP in standing, horizontal supine, and 6° HDT postures. The purpose of the studies was to assess effects of space flight on cardiovascular responses to orthostasis (Buckey et al., in revision), and to compare effects of microgravity and 6° HDT on cardiac filling pressure (Buckey et al., 1993; Buckey et al., in press). As a co-investigator on the human SLS experiment "Cardiovascular adaptation to microgravity" (E-294; PI: C. Gunnar Blomqvist), I had a direct role in preparations for and acquisition and interpretation of CVP measurements before, during, and after the two SLS space flights (Buckey et al., 1993; Buckey et al., in press). The results presented here constitute part of the data in two articles submitted to the

Journal of Applied Physiology for publication (Buckey et al., in press; Buckey et al., in revision).

We studied four healthy subjects after they provided written informed consent to participate (3 males, 1 female; ages: 35–50 years; weights: 64–81 kg; heights: 169–181 cm). The procedures and protocol were approved by human research committees at the NASA Johnson Space Center, Houston, Texas, and the University of Texas Southwestern Medical Center, Dallas, Texas. All data collection took place at Johnson Space Center or at Kennedy Space Center, Florida. Subjects were instructed to avoid alcohol and medications for at least 24 hours prior to the study.

Subjects were catheterized with a 4F polyurethane fluid-filled catheter inserted through the median cubital vein into the superior vena cava near the right atrium under fluoroscopic guidance. Sterile procedures were employed throughout catheterization. The catheter was placed with a peel-away introducer system developed in conjunction with Cook, Inc. A standard 16 gauge intravenous catheter is placed in the median cubital vein. The trocar is removed, leaving the plastic catheter in place. A guide wire is then inserted through the catheter, which is then withdrawn, leaving the guide wire in the vein. The CVP catheter introducer/vein dilator is then inserted over the

guide wire, and the guide wire is withdrawn, leaving the plastic introducer in the arm vein. The CVP catheter is then inserted and advanced through the introducer and arm veins into the superior vena cava, using minimal fluoroscopy as necessary. A longer guide wire may be inserted within the CVP catheter at this stage to stiffen and thus help advance the catheter. After satisfactory intrathoracic positioning of the CVP catheter, the plastic introducer is withdrawn from the insertion site and peeled away from around the CVP catheter, leaving only the CVP catheter placed transcutaneously in the arm. Betadine ointment is dabbed over the insertion site, which is then covered with a sterile Op-Site transparent plastic dressing. The remainder of the catheter is then taped in place to the arm for connection to the CVP measuring system.

CVP was measured directly in the superior vena cava to  $\pm 0.1$  mmHg using a system designed for ambulatory measurement of CVP (SMCVP; Buckey et al., 1991; see Appendix A). This system was specially designed for use in space flight conditions, and was extensively tested for safety, accuracy, and reliability. SMCVPs were manually calibrated with fluid manometers filled with isotonic saline. The fluid-filled CVP catheter was connected to an SMCVP. Fluoroscopic visualization of the catheter tip and right atrium permitted accurate external positioning of the SMCVP pressure transducer just below the right

axilla. Valsalva and Mueller respiratory maneuvers by the subject ensured intrathoracic catheter positioning and proper SMCVP function.

CVP was measured while supine and after stabilization upon standing (within 1 min). Subjects stood from a gurney with equal weight on each foot, and they remained still for at least 1 min after standing. During a separate experimental session, CVP was measured during the transition from horizontal supine to  $6^\circ$  HDT posture on a tilting bed. The SMCVP signal was recorded on an Astromed MT 95000 chart recorder and/or a Racal VHS data tape recorder.

**3.4.1 Results—** In the four subjects we studied, pre-standing supine CVP averaged  $9.7 \pm 0.7$  mmHg (mean  $\pm$  SE), and standing ( $1.0 G_z$ ) values averaged  $2.9 \pm 0.8$ , giving a mean reduction of  $6.8 \pm 0.9$  mmHg in CVP upon standing from horizontal supine posture (fig. 3-3). In 10 subjects, Katkov and Chestukhin (1980) reported right atrial pressure of  $5.6 \pm 0.7$  in horizontal recumbency, and  $-0.9 \pm 0.4$  mmHg at  $75^\circ$  HUT ( $0.97 G_z$ ), giving a mean right atrial pressure reduction of 6.5 mmHg upon HUT (fig. 3-3). In two of our subjects, pre-HDT supine CVP averaged  $8.0 \pm 0.7$  mmHg, and increased to  $8.9 \pm 0.6$  mmHg immediately upon initiation of  $6^\circ$  HDT, for an average increase of  $0.9 \pm 0.1$  mmHg. A  $6^\circ$  HDT average right atrial pressure for Katkov and

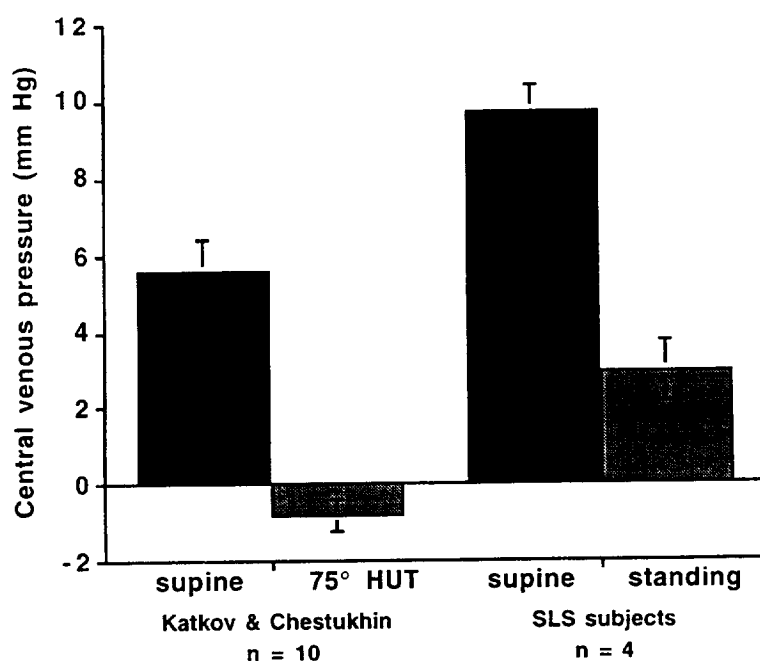


Figure 3-3. Supine and  $75^\circ$  HUT right atrial pressure found by Katkov and Chestukhin (1980;  $n = 10$ ), and supine and standing central venous pressure in four SLS subjects (mean  $\pm$  SE). The two studies found similar average supine-to-upright venous pressure reduction (6.5–6.8 mmHg).

Chestukhin's data was calculated by interpolating linearly between 0° supine and 10° HDT ( $-0.17 G_z$ ) means. This average equaled 6.4 mmHg, so the increase they would have observed between horizontal supine and 6° HDT right atrial pressures would average 0.8 mmHg. Although the subjects we studied tended to be older (35–50 years of age) than those studied by Katkov and Chestukhin (29–40 years), mean height and weight of the two subject groups were similar.

As was seen in the leg venous pressure data (above), the supine-to-standing and supine-to-HDT changes in CVP seen in our studies agree very well with the right atrial pressure changes reported in Katkov and Chestukhin (1980; fig. 3-3), and it is the *changes* in pressure which are important to calculation of compliance. Again, differences between the two studies in absolute values of pressure probably result from differences in transducer leveling technique. As in the leg, CVP measurements stabilize within several seconds of a change in posture or tilt angle if the subject remains still (Pollack and Wood, 1949; unpublished observations).

### 3.5 Few Other Studies Exist of Jugular Venous Pressure in Healthy Subjects

Unlike the literature concerning leg venous pressure measurements, most studies of upper body venous responses to gravity have been performed on patients. Among his patients, Avasthey (1972) also measured right atrial and jugular venous pressures in five normal subjects while supine and within 1 min of standing. Although the findings were presented in a relatively descriptive fashion (graph with no averages or measures of variation), results were in good agreement with Katkov and Chestukhin (1980): Avasthey (1972) reported supine-to-standing reduction of internal jugular venous pressure equaling 4–5 mmHg, while Katkov and Chestukhin (1980) found supine-to-75° HUT reduction of internal jugular venous pressure averaging 5.1 mmHg. Also, several studies in patients demonstrate that changes in CVP relate well with changes in jugular venous pressure, and that jugular venous pressures consistently exceed CVP, particularly while upright, because the jugular veins tend to collapse at the relatively negative thoracic entrance in upright postures (Barth, 1971; Avasthey, 1972; Briscoe, 1973; Stoelting, 1973; Reynolds et al., 1984; Shah et al., 1986). Interestingly, with the chest open the correlation between central and jugular venous pressures decreases, but remains significant, relative to chest-closed conditions (Briscoe, 1973). Agreement between the CVP findings reported in 3.4.1, the literature, and data of Katkov and Chestukhin (1980) in upper body sites supports use of

Katkov and Chestukhin's jugular venous pressure data for calculation of neck venous compliance.

The relative lack of studies of jugular venous pressure in normal subjects probably results from the greater risks imposed by near-thoracic and intrathoracic catheterization. For example, jugular venous pressures may decrease below atmospheric levels during inspiration in upright posture, such that leakage in a jugular vein catheter or pressure measurement system could cause air embolism. In fact, this risk explains and defends the common clinical practice of tilting patients 10–20° head-down for jugular or subclavian vein catheterization procedures. Therefore, investigators rarely perform studies employing such procedures in healthy subjects because, unlike patients, healthy subjects derive no clinical benefit from such procedures.

### 3.6 Conclusion

Data from Aratow et al. (1993b), Buckey et al. (in press and in revision), unpublished observations reported here, and the scientific literature collectively confirm and validate venous pressure findings of Katkov and Chestukhin (1980), and provide strong support for use of their data to calculate and thus compare leg and neck venous compliance. Therefore, I have employed their data to test my primary hypothesis in section 4. Normal gravitational changes in calf venous pressure substantially exceed those changes in neck venous pressure. Such regional differences in vascular pressure and pressure variation drive the differences in local vascular function which are the subject of this report.

## 4. Does Upper Body Venous Compliance Exceed Lower Body Venous Compliance in Humans?

The hydrostatic indifference level (HIL) is that site in the circulation where hydrostatic pressure remains constant with acute changes in orientation of the organism to gravity (Clark et al., 1934; Gauer and Thron, 1965; Watenpaugh and Hargens, 1995). In humans, the venous HIL resides 5–8 cm below the diaphragm (Gauer and Thron, 1965). This relatively headward positioning of the HIL serves to maintain cardiac filling (central venous) pressure during orthostasis, because filling pressure decreases according to the vertical distance between the heart and the HIL (see sec. 1 and fig. 1-2). HIL location depends hypothetically on relative vascular compliances in the circulation, such that the HIL moves away from regions of low compliance toward regions of high

compliance. Human leg venous compliance should be low to prevent excessive pooling of blood and reduction of cardiac filling pressure during orthostasis, yet little physiologic need exists for low venous compliance in the upper body. In fact, low venous compliance in the upper body would push the HIL footward during orthostasis, and thus counteract the headward HIL positioning imposed by low leg venous compliance.

In spite of this theoretical foundation for HIL positioning, no evidence exists that venous compliance is indeed lower in the lower body than in the upper body. At the tissue level, Kirsch et al. (1980b) demonstrated regional differences in human cutaneous tissue compliance: they used a miniature plethysmograph (Kirsch et al., 1980a) to show that skin over the frontal bone, sternum (T3 level) or vertebral column (T9–11) was 1.5 to 3 times more compliant than skin over the tibia. Upper and lower body macrovascular compliances have not been compared. Therefore, we hypothesized that venous compliance of the neck exceeds that of the calf in humans. The calf and neck were chosen as comparable, representative sites in the lower and upper body, respectively, because they are both composed largely of skin and skeletal muscle. To test the differential compliance hypothesis, whole-body tilting was employed to use gravity to alter local venous pressures. Stepwise tilting from head up to head down generates stepwise physiologic increments in neck venous pressure, whereas tilting from head down to head up increases calf venous pressure (Katkov and Chestukhin, 1980; see sec. 3).

#### 4.1 Methods

To compare regional venous compliances, we measured calf and neck volume changes during whole-body tilting in nine healthy subjects (table 4-1). Standing calf circumference of these subjects (as measured with a tape measure) averaged  $36.6 \pm 2.9$  cm (mean  $\pm$  SD), and neck circumference averaged  $34.6 \pm 4.5$  cm. The NASA Ames Research Center Human Research Institutional Review Board approved the protocol, and subjects gave their informed consent to participate. Subjects avoided caffeine, alcohol, medications, and heavy exercise at least 24 hours before their participation.

Calf and neck volume data were collected during tilting at the following angles (Breit et al., 1993; Watenpaugh et al., 1993; see sec. 2):  $90^\circ$  (HUT),  $54^\circ$ ,  $30^\circ$ ,  $12^\circ$ ,  $0^\circ$  (horizontal supine),  $-6^\circ$  (HDT),  $-12^\circ$ ,  $-6^\circ$ ,  $0^\circ$ ,  $12^\circ$ ,  $30^\circ$ ,  $54^\circ$ , and  $90^\circ$ . These tilt angles elicit  $G_z$  stimulation equal to their sine, such that  $90^\circ = 1.0G_z$ ,  $54^\circ = 0.8G_z$ ,  $30^\circ = 0.5G_z$ ,  $12^\circ = 0.2G_z$ ,  $0^\circ = 0.0G_z$ ,  $-6^\circ = -0.1G_z$ , and  $-12^\circ = -0.2G_z$  (Breit et al., 1993). The padded tilt table was equipped with a footplate, and subjects were secured

to the table with a wide strap placed snugly across the upper abdomen. We measured volume changes in 1 cm thick calf and neck segments with electronically calibrated Hg- or Ga/In-in-silastic strain gauge plethysmography (Whitney, 1953; Watenpaugh, 1991). Strain gauges were placed on the left calf at its maximal girth, and around the neck 1 cm distal to the hyoid. Subjects remained relaxed and still throughout data collection, and foam cushions (5 cm thick) supported the legs and head to ensure comfort, to help prevent any leg or neck movement during tilting, and to prevent contact between the strain gauges and the tilt table. Subjects were not allowed to talk or sleep during data collection. Leg and neck volume data were collected with an IBM-compatible computer, an analog-to-digital board (Metrabyte, Taunton, Massachusetts), and data acquisition software (Labtech Notebook, Wilmington, Massachusetts), and were averaged over the last 5 sec of each 30 sec tilt position interval.

Table 4-1. Descriptive characteristics of subject groups studied for calf and neck venous pressure (Katkov and Chestukhin, 1980) and volume measurements (the present study) during whole-body tilting (means  $\pm$  SD)\*

	Katkov and Chestukhin	Present study
Sample size	10	9
Gender	all male	5 male, 4 female
Age range (yr)	29 – 40	20 – 47
Height (cm)	$174 \pm 4$	$169 \pm 8$
Weight (kg)	$71.3 \pm 4.3$	$64.7 \pm 12.6$

\*No significant differences exist between the groups, except that the Katkov and Chestukhin group was all male.

Venous compliance was calculated as the slope of the segment volume/local venous pressure relationship. For venous pressure data at the sites of interest, we used jugular and leg venous pressure data collected during whole-body tilting by Katkov and Chestukhin (1980; see sec. 3). The age range of subjects employed in the present study encompassed that of the subjects employed by Katkov and Chestukhin (1980), and independent t-tests ( $\alpha = 0.05$ ; Zar, 1984) determined that average height and weight of the two subject groups were similar (table 4-1). Katkov and Chestukhin (1980) also reported that their subjects were healthy. They employed only male subjects, whereas we studied male and female subjects. Therefore, combining their data with ours to calculate compliance

assumes that the physical laws of gravitational hydrostatics operate similarly in men and women, which is reasonable.

Where we employed tilt angles different from those employed by Katkov and Chestukhin (1980), we linearly interpolated their venous pressure data according to the sine of the tilt angles ( $G_z$  levels) we employed (table 4-2).

Table 4-2. Calf and neck venous pressure (VP) data from Katkov and Chestukhin (1980) during whole-body tilting, linearly interpolated as necessary to fit our experimental conditions\*

Tilt table angle (°)	$G_z$ (sin[tilt angle])	Calf VP (mmHg)	Neck VP (mmHg)
-12	-0.2	10.7	13.5
-6	-0.1	14.0	10.7
0	0.0	17.9	7.9
12	0.2	22.1	4.5
30	0.5	38.8	3.0
54	0.8	55.0	–
90	1.0	65.0	–

\*These interpolations assume that the physical laws of gravitational hydrostatics remain in force between the femoral and foot veins and at all tilt angles. Above 30° HUT, neck (jugular) venous pressure did not change significantly, and was thus not used for venous compliance calculation. Over the range of tilt used in this study, Katkov and Chestukhin (1980) reported average standard deviations of 0.6 mmHg for neck venous pressure, and 2.0 mmHg for leg venous pressures.

Also, we interpolated linearly between their femoral (groin level) and foot venous pressure measurements to derive venous pressures in the calf at the level of its maximum girth. The level of maximum calf girth averaged 64% of the distance from the femoral vein (groin level) to the foot in our subjects. For neck (jugular) venous pressures, only the  $G_z$  interpolation was necessary, because our volume measurements were made at approximately the same site as Katkov and Chestukhin's pressure measurements. The only assumption involved in the above interpolations is that the physical laws of gravitational hydrostatics remain in force between the femoral and foot veins and at all tilt angles, which is reasonable. Furthermore, our direct measurements of leg and central venous pressures (Aratow et al., 1993b; Buckey et al., in press; Buckey et al., in revision; unpublished observations), and other results from the literature validate this approach (see sec. 3).

Regression analyses were performed to quantify and assess linearity of venous compliance slopes from each site, and a paired t-test evaluated whether sites exhibited different average compliance slopes ( $\alpha = 0.05$ ; Zar, 1984). Regression analyses did not include interindividual variation in venous pressure data because raw data of Katkov and Chestukhin (1980) were not collected in our subjects. However, Katkov and Chestukhin (1980) reported relatively low interindividual variability in local venous pressures (average standard deviations of 0.6 mmHg for neck venous pressure, and 2.0 mmHg for leg venous pressures), and the subject group in the present study exhibited similar mean height and weight to Katkov and Chestukhin's subject group (see table 4-1). Therefore, omission of venous pressure variability in the present regression analyses was considered benign to testing of the hypothesis.

Venous compliance values were multiplied by 100 for convenience. Data are presented as means  $\pm$  SE. Calculations and statistical analyses were performed with Excel (Microsoft, Inc.), Abstat (Anderson-Bell, Inc.), and Statistica (Statsoft, Inc.) procedures.

## 4.2 Results

We found that mean calf venous compliance equaled  $4.6 \pm 1.0 \text{ ml} \times \text{mmHg}^{-1} \times 10^2$  ( $n = 9$ ; mean  $\pm$  SE), whereas neck venous compliance was 6-fold greater at  $27.9 \pm 4.5 \text{ ml} \times \text{mmHg}^{-1} \times 10^2$  (fig. 4-1). When local venous compliance assessment was limited to the pressure range common to both sites (10–15 mmHg), neck venous compliance still exceeded calf venous compliance by a factor of 4.8. All subjects exhibited significant segment volume/pressure relationships at both sites, and venous compliance slopes for both sites displayed similar linearity in all subjects (calf  $r^2 = 0.93 \pm 0.02$ ; neck  $r^2 = 0.93 \pm 0.02$ ). Standard error of the individual slopes averaged  $0.5 \text{ ml} \times \text{mmHg}^{-1} \times 10^2$  at the calf and  $4.1 \text{ ml} \times \text{mmHg}^{-1} \times 10^2$  at the neck. Segment volume standard errors ranged from 5.2 to 5.4 ml at the calf, and from 8.0 to 8.3 ml at the neck. In contrast to relatively large interindividual variation, intraindividual coefficients of variation for segment volumes in two subjects undergoing three repeated tilting procedures equaled 0.3% (0.003) or less.

Neither calf nor neck venous compliance correlated with height, weight, or age, and gender did not affect venous compliance (all  $p > 0.2$ ). Calf and neck venous compliance did correlate significantly with each other ( $r^2 = 0.56$ ; fig. 4-2). Calf circumference tended to exceed neck circumference ( $p = 0.07$ ).

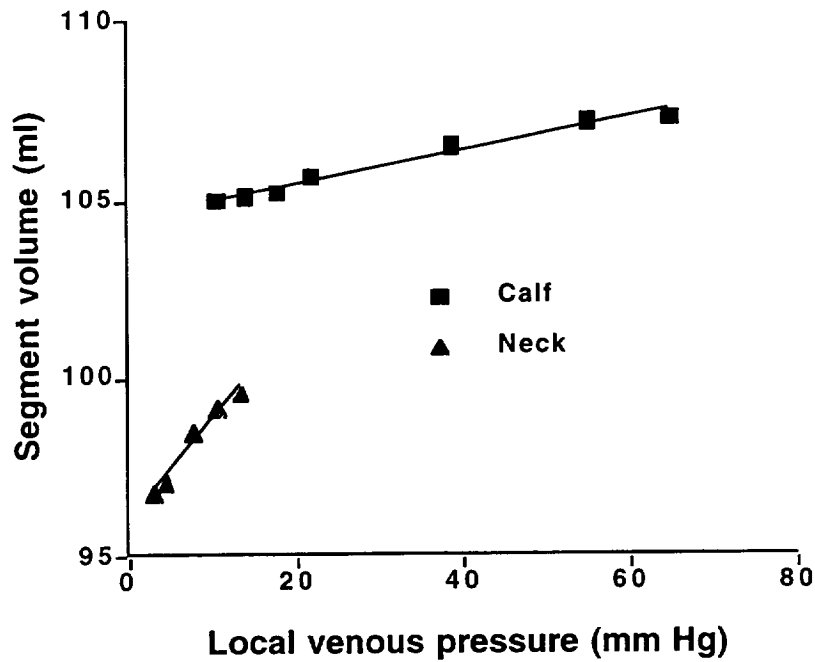


Figure 4-1. Plot of mean segment volume vs. local venous pressure for the calf (squares) and neck (triangles) during whole-body tilting ( $n = 9$ ). Local venous compliance equals the slope of the volume/pressure relationship. Neck venous compliance exceeded calf venous compliance by a factor of 6.1. Segment volume standard errors ranged from 5.2 to 5.4 ml at the calf, and from 8.0 to 8.3 ml at the neck. Individual volume/pressure regressions were all significant at each site (mean  $r^2 = 0.93 \pm 0.02$ ).

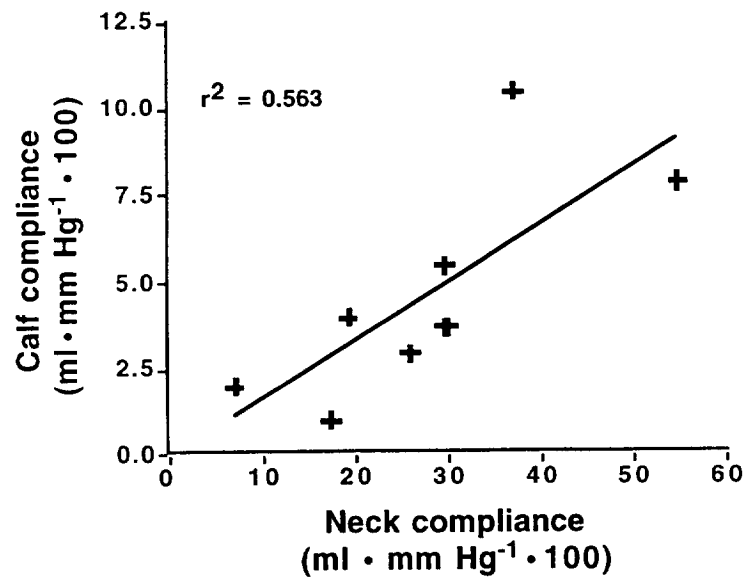


Figure 4-2. Calf and neck venous compliance correlated positively with one another ( $r^2 = 0.56$ ). Subjects with relatively greater neck venous compliance also exhibited relatively greater calf venous compliance.

### 4.3 Discussion

These results clearly demonstrate that the distensibility of veins in the human neck substantially exceeds the distensibility of veins in the calf (fig. 4-1), even when local venous pressure changes are similar. It is possible that neck venous compliance would decrease at calf-like venous pressures ( $>20$  mmHg), yet neck veins rarely experience such pressures: Katkov and Chestukhin (1980) measured jugular venous pressures  $> 20$  mmHg only at HDT angles  $> 30^\circ$ . Over the range of tilt used in this study, neck volume elevation consistently exceeded the absolute magnitude of calf volume reduction, in spite of the larger venous pressure changes experienced in the calf (see sec. 2). Therefore, these results indicate that marked head-to-foot reduction of venous compliance exists in humans, as predicted by the hydrostatic indifference level concept.

Clark and co-workers (1934) first introduced the HIL concept. They noted that upright human foot and dog hindlimb venous pressures were consistently less than would be predicted by the vertical distance from the heart, and they concluded that a noncardiac reference point must exist in the venous circulation where pressures do not change with orientation of the organism in gravity. They stated that the HIL "may be anywhere in the venous system, depending on the relative elasticity of its different parts." Gauer and Thron (1965) found the human venous HIL to be 5–8 cm below the diaphragm using HUT from horizontal posture yet, until the present report, no upper versus lower body venous compliance comparisons existed to explain this relative headward positioning of the HIL. Subjects in our study with relatively greater neck venous compliance also exhibited relatively greater calf venous compliance (fig. 4-2). This trend agrees with the regional compliance differential/HIL concept in that there should be an optimal ratio of upper-to-lower body venous compliance for positioning of the HIL towards the heart. Our data indicate this ratio is about 6 when using the neck and calf as representative upper and lower body sites, respectively. Because the legs probably possess a much larger venous capacity than sites headward from the heart, it may be relatively more important for legs to exhibit low venous compliance than for upper body sites to exhibit high venous compliance to maintain heartward HIL positioning.

HUT on a tilt table with a footplate requires a certain degree of calf muscle activation to accommodate the footward force imposed by gravity. Such muscle activation conceivably could reduce calf venous compliance. However, this calf muscle activation is minimal ( $<10\%$  of maximal voluntary levels; Kelton and Wright, 1949; Basmajian and Bentzon, 1954; Basmajian, 1985;

Alexander, 1992; Murthy et al., 1994a), and produces minimal calf volume change ( $<0.3\%$ ; Barendsen and van den Berg, 1984). Furthermore, we have demonstrated that calf venous compliance measured with HUT equals compliance measured with conventional venous occlusion plethysmography in relaxed legs of supine subjects (Watenpaugh et al., in review; see sec. 5). Calf venous compliance values reported here also agree with others reported in the venous occlusion literature, which range from  $3.0 \text{ ml} \times \text{mmHg}^{-1} \times 10^2$  (Convertino et al., 1988) to  $7\text{--}8 \text{ ml} \times \text{mmHg}^{-1} \times 10^2$  (Kidd and Lyons, 1958). Therefore, the disparity between calf and neck venous compliance is not simply due to HUT-induced leg muscle activation.

It is unlikely that tracheal volume changes contribute to neck venous compliance, because the cartilaginous trachea, like bone, is noncompliant relative to skin, muscle, and other "soft" tissues. It is also improbable that capillary filtration (i.e., extravascular tissue volume elevation) substantially contributed to calf or neck venous compliance, due to the short duration (30 sec) spent at each tilt table angle. Multiple studies have shown that the relative contribution of capillary filtration to tissue volume elevation increases with the duration of an intravascular pressure increase (Schnizer et al., 1978; Vissing and Nielsen, 1988; Watenpaugh et al., in press).

Unlike the human leg vasculature, the upper body circulation is not continually challenged with and therefore not well adapted to large gravitational pressure changes (Hargens et al., 1992). Furthermore, major leg veins are probably more deeply embedded in skeletal muscle (Buckey et al., 1988; Convertino et al., 1988), and for that reason may display less compliance than veins in the neck. Therefore, the relatively low calf venous compliance probably results from stiffer venous, skeletal muscle, and connective tissues, and better-developed local and central neural controls of venous distensibility. The relative contributions of these factors require further study. The human microcirculation exhibits similar regional adaptations to gravity (Williamson et al., 1975; Breit et al., 1993). Also, regional vascular adaptations to gravity appear in giraffes and other tall, upright terrestrial animals (Hargens et al., 1987 and 1988; Seymour et al., 1993), and are probably reversed in animals such as bats and sloths, which spend substantial portions of their existence in head-down positions.

Other differences exist between human upper and lower body vascular structure and function. Leg veins exhibit more longitudinal smooth muscle development than arm veins (Cooper, 1981). Lower body capillary basement membranes in skeletal muscle are thicker than those in

the upper body (Williamson et al., 1975), presumably to help restrict lower body capillary filtration in the face of the greater capillary pressures experienced in the lower body while upright (Levick and Michel, 1978). Atrial natriuretic peptide increases capillary filtration in the forearm and splanchnic circulation, yet the peptide decreases leg capillary filtration (Watenpaugh et al., in press). The present findings agree qualitatively with the upper-to-lower body compliance reduction reported by Kirsch et al. (1980b) in cutaneous tissues, yet the regional disparity we observed was about two to three times greater than what they found. This quantitative difference probably stems from the larger mechanical stress imposed by gravitational pressures in the circulation relative to surrounding tissues.

Humans commonly experience orthostatic intolerance after space flight (Watenpaugh and Hargens, 1995) and bed rest (Fortney et al., 1995). Degradation of regional vascular adaptations in microgravity or bed rest (increased lower body venous compliance and/or reduced upper body venous compliance) may compromise orthostatic tolerance by shifting the venous HIL further below the heart. Such a shift compromises cardiac function during an orthostatic challenge, because cardiac filling pressure decreases to a greater extent than if the HIL is nearer the heart. Prolonged bed rest and space flight probably increase leg venous compliance via tissue dehydration, and through loss of leg vascular and skeletal muscle mass and function (Thornton and Hoffler, 1977; Watenpaugh and Hargens, 1995). In addition, HDT and microgravity may reduce upper body tissue and venous compliance by favoring upper body transcapillary filtration (Parazynski et al., 1991), and by inducing functional and structural changes to accommodate chronic local vascular pressure elevation. Whether bed rest and space flight reduce the normal head-to-foot gradient of venous compliance, and how much such effects contribute to orthostatic intolerance, remains to be quantified.

## 5. Does Calf Venous Compliance During Head-Up Tilt Differ from Supine Relaxed Calf Venous Compliance?

Elevated calf venous compliance may contribute to human orthostatic intolerance following space flight and bed rest (see sec. 1). Calf venous compliance is measured conventionally with venous occlusion plethysmography in supine subjects (Whitney, 1953; Siggaard-Andersen, 1970). With this well-established technique, subjects undergo inflation of a pressure cuff around the thigh just proximal to the knee, which increases calf venous pressure. A plethysmograph simultaneously measures calf volume elevation. Calf venous compliance equals calf

volume elevation per mmHg thigh occlusion (calf venous) pressure in relaxed legs of the supine subjects. Compliance may also be measured during stepwise HUT as calf volume elevation per mmHg *gravitational* venous pressure elevation produced by HUT (see sec. 4). When considering cardiovascular responses to gravity, such an approach is more physiologically relevant than supine venous occlusion assessment of calf venous compliance, because gravity per se elicits calf venous pressure increments during HUT. However, during HUT on a tilt table with a footplate, calf muscles activate to counteract gravity: this is an obvious and natural response to gravitational force. Such muscle activation conceivably could reduce calf venous compliance, yet relatively little calf muscle activation occurs during HUT and orthostasis in humans (<10% of maximal voluntary levels; Kelton and Wright, 1949; Basmajian and Bentzon, 1954; Basmajian, 1985; Alexander, 1992; Murthy et al., 1994a). Also, this activation produces minimal calf volume change (<0.3%; Barendsen and van den Berg, 1984). To determine whether this minimal calf muscle activation which occurs during HUT has any important effect on human calf venous compliance, we compared calf venous compliance findings from the previously described HUT study (sec. 4) to those from conventional supine venous occlusion assessments of relaxed calf compliance. We hypothesized that calf venous compliance measured with HUT equals that measured with supine venous occlusion.

### 5.1 Methods

Section 4 presented methods for HUT measurement of calf venous compliance. For supine venous occlusion measurement of calf venous compliance, 14 additional, similar subjects participated. Physical examinations indicated these subjects were also in excellent health. Table 5-1 presents characteristics of the supine venous occlusion and HUT subject groups. Subjects provided informed consent before participating in this study, and the protocols received Institutional Review Board approval at the NASA Ames Research Center and Johnson Space Center, and at the University of Texas Southwestern Medical Center. Subjects avoided caffeine, alcohol, medications, and heavy exercise for at least 24 hours prior to their participation.

Supine subjects were instrumented with either a mercury-in-silastic strain gauge or another similar plethysmograph (Buckey et al., 1985; see Appendix B) to measure increase of left calf volume. Preliminary studies found that (predictably) no difference exists in right and left calf venous compliance. The plethysmograph was positioned around the calf at its maximum girth. A

Table 5-1. Descriptive characteristics and calf venous compliance of subject groups studied with venous occlusion and whole-body tilting (means  $\pm$  SD)

	Venous occlusion	Head-up tilt
Sample size	14	9
Gender	5 F, 9 M	4 F, 5 M
Age range (yr)	25 – 50	20 – 47
Height (cm)	172 $\pm$ 7	169 $\pm$ 8
Weight (kg)	71.4 $\pm$ 7.8	64.7 $\pm$ 12.6
Calf circumference (cm)	36.3 $\pm$ 2.5	36.6 $\pm$ 2.9
Calf compliance (ml $\times$ mmHg <sup>-1</sup> $\times$ 10 <sup>2</sup> )	4.7 $\pm$ 1.6	4.6 $\pm$ 3.0

contoured thigh cuff (Hokansen, Inc.) was connected to a compressed air tank via a pressure regulator, and was positioned just proximal to the left knee. This cuff allowed controlled elevation of calf venous pressure. The left leg was elevated approximately 15° above horizontal on foam cushions, with the knee comfortably bent.

Subjects were supine between 10 and 30 min prior to data collection. The venous occlusion protocol consisted of 20, 40, 60, and 80 mmHg thigh cuff inflations held for 1, 2, 3, and 4 min, respectively (Watenpaugh et al., 1989); 1 min of cuff deflation to 0 mmHg separated occlusions. Subjects remained relaxed and still during data collection; however, they were not allowed to talk or sleep. To assess repeatability of supine venous occlusion compliance measurement, seven subjects underwent the venous occlusion protocol twice in the same session, and at up to three sessions separated by one month.

Calf volume elevation was determined at the end of each occlusion period (i.e., at the end of the single minute of 20 mmHg occlusion, at the end of the second minute of 40 mmHg occlusion, etc.). Differences in volume elevation at different pressures were then divided by the differences between pressures (i.e., the slope of the compliance relationship was calculated) to determine calf venous compliance. Regression analyses were performed to assess linearity of compliance slopes from each method (HUT and venous occlusion). Independent t-tests evaluated similarity of the supine venous occlusion and HUT subject groups, and whether HUT and supine venous occlusion produced different average compliance slopes and slope linearity ( $\alpha = 0.05$ ; Zar, 1984). For comparison of slope linearity,  $r^2$  values were arcsine-transformed to ensure normality of distribution. Correlations were

attempted between calf venous compliance and other subject characteristics. Compliance values were multiplied by 100 for convenience. Data are presented as means  $\pm$  SD except where noted. Calculations and statistical analyses were performed with Excel (Microsoft, Inc.), Abstat (Anderson-Bell, Inc.), and Statistica (Statsoft, Inc.) procedures.

## 5.2 Results

Calf venous compliance slope measured with HUT ( $4.6 \pm 3.0$  ml  $\times$  mmHg<sup>-1</sup>  $\times$  10<sup>2</sup>;  $n = 9$ ) essentially equaled that measured with venous occlusion in supine subjects ( $4.7 \pm 1.6$  ml  $\times$  mmHg<sup>-1</sup>  $\times$  10<sup>2</sup>;  $n = 14$ ; table 5-1). Standard error of the individual slopes per se averaged  $0.5$  ml  $\times$  mmHg<sup>-1</sup>  $\times$  10<sup>2</sup> for both methods. Volume/pressure relationships for both methods displayed linearity in all subjects (venous occlusion  $r^2 = 0.98 \pm 0.03$ ; HUT  $r^2 = 0.93 \pm 0.07$ ), with arcsine-transformed  $r^2$  being significantly greater for venous occlusion than for HUT. To facilitate comparison, figure 5-1 illustrates percent increase in calf volume (mean  $\pm$  SE) plotted against calf venous pressure for each method. Like the raw volume data, the percent volume change data exhibit slope similarity between methods. Although the percent y-intercepts appear different, intercepts from the volume/pressure relationships established with volumetric (non-percent) data were similar between the methods due to intersubject variation in calf size (circumference data, table 5-1). The two subject groups possessed similar age range, height, weight, calf circumference, and gender composition (table 5-1). Height, weight, and age did not correlate with calf venous compliance as measured with either method, nor did gender significantly affect calf venous compliance. Calf venous compliance correlated positively with calf circumference during venous occlusion ( $r^2 = 0.33$ ), but not during HUT. In seven subjects who underwent multiple repeated measures of supine venous occlusion calf venous compliance, the coefficient of variation averaged 15.0%.

## 5.3 Discussion

These results clearly demonstrate that human calf venous compliance as measured during HUT does not differ from that measured with venous occlusion in supine, relaxed subjects. The subject groups studied with each method were similar in terms of sample size, gender ratio, age range, height, weight, and calf circumference, so the comparison of the two methods in different subject groups is valid. Thus, it appears that the minimal calf muscle activation associated with HUT does not importantly affect calf venous compliance.

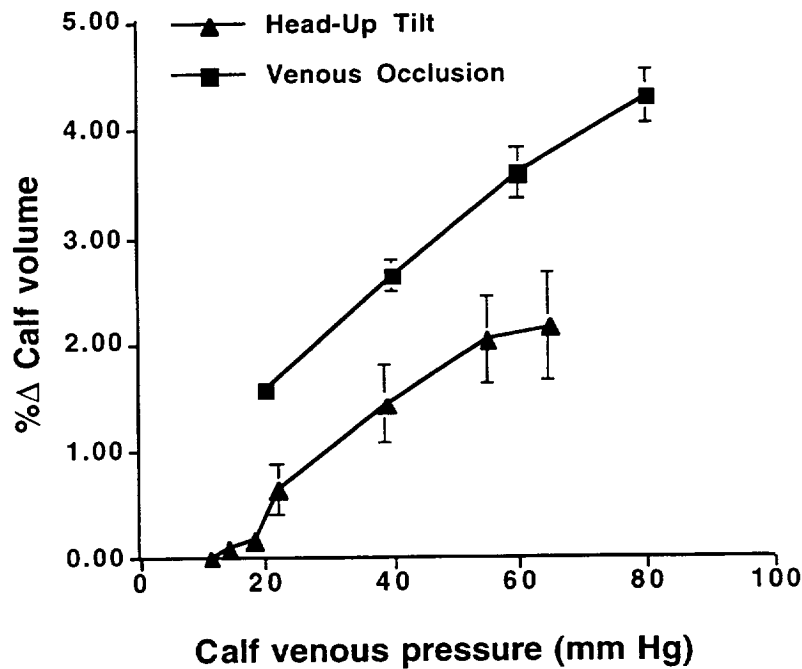


Figure 5-1. Percent increase in calf volume (means  $\pm$  SE) plotted against calf venous pressure for supine venous occlusion (squares,  $n = 14$ ) and HUT (triangles,  $n = 9$ ) calf venous compliance assessments.

Other studies support this contention. Human leg muscles (soleus, gastrocnemius and tibialis anterior) generate little or no electromyographic activity while standing (Kelton and Wright, 1949; Basmajian and Bentzon, 1954; Alexander, 1992; Basmajian, 1985). Some phasic activity results from muscle activation necessary to maintain balance, but this activity is very small compared to that seen during locomotion and effort. Also, Murthy et al. (1994a) reported supine-to-standing intramuscular pressure elevation averaging 27 mmHg in leg muscles (soleus and tibialis anterior). This increase is small compared to the peak intramuscular pressures of 200–400 mmHg observed in these muscles during locomotion (Murthy et al., 1994a) and maximal effort (Aratow et al., 1993a). Standing is a biomechanically and metabolically economical posture in humans (Basmajian, 1985).

All of the above upright electromyographic and intramuscular pressure measurements were made during free, unsupported standing. However, in most tilt table studies, including the present, a wide strap secures subjects to the table so that they remain stable during tilting. This stability eliminates the need for subjects to maintain balance during orthostasis, and thus probably further reduces leg muscle activity while upright. Supine lower body negative pressure (LBNP) against a footplate

imposes loads on leg muscles similar to upright posture, yet requires little or no balance function (Hargens et al., 1991; Murthy et al., 1994b). Paradoxically, leg volume elevation during stepwise LBNP with a footplate (i.e., calf venous compliance as calf volume elevation per mmHg LBNP =  $7.0 \text{ vol}\% \times \text{mmHg}^{-1} \times 10^2$ ) appeared somewhat greater than during LBNP with a saddle ( $5.5 \text{ vol}\% \times \text{mmHg}^{-1} \times 10^2$ ), which allows the legs to remain relaxed (Watenpaugh et al., 1994). Finally, it should be noted that during whole-body tilting, the legs support body weight in proportion to the sine of the tilt angle, which is less than 1 at all tilt angles less than  $90^\circ$ . For example, at  $30^\circ$  HUT, leg muscle activation should be about half of levels seen at  $90^\circ$  HUT ( $\sin(30) = 0.5$ ).

Calf venous compliance values reported here agree with those reported in the venous occlusion literature, which range from  $3.0 \text{ ml} \times \text{mmHg}^{-1} \times 10^2$  (reported in units of  $\text{vol}\% \times \text{mmHg}^{-1} \times 10^2$ ;  $n = 10$ ; Convertino et al., 1988) to  $7\text{--}8 \text{ ml} \times \text{mmHg}^{-1} \times 10^2$  ( $n = 8$ ; Kidd and Lyons, 1958). The apparent offset (intercept difference) between HUT and venous occlusion % $\Delta$  compliance slopes (fig. 5-1) results from the fact that about 1–2% calf volume elevation occurs before calf venous pressure approaches the occlusion cuff pressure. This occurs because leg veins are relatively empty in the supine leg-elevated position employed for venous occlusion

plethysmography, and arterial inflow must fill the veins before their compliance characteristics become apparent with venous occlusion (Siggaard-Andersen, 1970). Such is not the case during HUT.

In spite of fundamental differences between the methods, they generated essentially identical venous compliance values, indicating that the differences are functionally unimportant when no other experimental interventions are involved. When used to test hypotheses, the two methods may have different utility. For example, the venous occlusion method may be more useful for pharmacology and resting cardiovascular studies, whereas whole-body tilting may be better suited to studies of orthostatic intolerance and gravity-related hypotheses. I conclude that the minimal calf muscle activation which occurs during HUT orthostasis does not importantly affect human calf venous compliance.

## 6. Conclusions

The findings presented above clearly indicate that human neck venous compliance substantially exceeds calf venous compliance (sec. 4). Therefore, the results indicate that marked head-to-foot reduction of venous compliance exists in humans, as predicted by the hydrostatic indifference level concept. The relatively low calf venous compliance probably results from stiffer venous and surrounding muscular and connective tissues, and better-developed neural controls of capacitance. Calf muscle activation during HUT apparently does not importantly affect calf venous compliance (sec. 5). Literature reports of calf and upper body venous pressures used in calculation of compliance were confirmed (sec. 3). Also, this report constitutes the first simultaneous use of neck and calf volume measurements to noninvasively quantify fluid shifts into and out of the upper and lower body, respectively (sec. 2), and the first use of tilt-induced gravitational pressure changes to quantify regional venous compliances. The data show that the leg is better adapted than the neck to resist venous distention with increased local venous pressures. Footward reduction of venous compliance is an appropriate and probably necessary adaptation to gravitational pressures in the human circulation. Therefore, relatively low leg venous compliance may be viewed as both a consequence of and a compensating mechanism for the high gravitational pressures experienced in the lower body circulation.

### 6.1 Future Related Research

Degradation of regional vascular adaptations in microgravity or bed rest (increased lower body compliance and/or reduced upper body compliance) may compromise

orthostatic tolerance by increasing footward pooling while upright. The HIL is not static, because relative regional compliances are not static. For example, if upper body venous compliance decreases, or if lower body venous compliance increases, the venous HIL would shift further below the heart. Such a shift compromises cardiac function during an orthostatic challenge, because cardiac filling pressure decreases to a greater extent than if the HIL is nearer the heart. HDT and microgravity may reduce upper body compliance by favoring upper body transcapillary filtration (Parazynski et al., 1991), and by inducing functional and structural changes to accommodate chronic local vascular pressure elevation. Reduction of compliance of upper body veins would hypothetically worsen central venous hypotensive effects of orthostasis by moving the HIL footward. Therefore, the research presented herein will provide a foundation for future assessment of whether bed rest and space flight reduce or eliminate the normal head-to-foot gradient of venous compliance, and whether such effects contribute to the orthostatic intolerance commonly seen after bed rest and space flight. Distinctions between superficial and deep veins, venous and tissue compliance, and between tissue types (splanchnic versus skeletal muscle, for example), and the systemic implications of such distinctions, may also be interesting.

Other upright terrestrial species such as giraffes, emus, ostriches, and arboreal snakes probably exhibit head-to-foot venous compliance reduction qualitatively similar to humans. Conversely, vertebrate species such as bats and sloths, which exist in predominantly head-down postures, probably display greater venous compliance in their legs than in headward regions. These ideas deserve investigation. Animal models also provide a means for assessing relative contributions of tissue-level factors underlying regional compliance variation (connective tissue differences, vascular versus skeletal muscle, neural mediation, etc.).

The human leg venous pressure literature and data presented herein (see sec. 3) indicate that venous valves apparently do not break venous blood columns in the body after even short periods of orthostasis; venous valves are probably most important to prevent retrograde flow in veins during activity, when pressures increase in surrounding skeletal muscle. If leg venous pressure during orthostasis indeed represents an unbroken proximal fluid column, then measurement of that pressure permits determination of the venous HIL, because pressure at any point below the HIL theoretically equals the vertical distance from the HIL (multiplied by blood density and the gravitational constant; Gauer and Thron, 1965; see sec. 1). It then becomes possible to determine how far the venous HIL is below the heart, and thus how

much cardiac filling pressure is reduced during orthostasis.

The same rationale applied in this report for the venous circulation also applies to the *arterial* circulation. It too has an HIL dependent theoretically on an upper-to-lower body reduction of vessel compliance (Gauer and Thron, 1965), yet this has not been assessed experimentally. If an arterial compliance gradient exists similar to that demonstrated herein for the venous circulation, then degradation of the arterial compliance gradient due to chronic loss of gravitational pressures during bed rest and space flight could compromise cerebral perfusion pressure during subsequent orthostasis.

Section 5 raises the interesting yet apparently unanswered question: what relationship exists between skeletal muscle contraction and venous or tissue compliance? A literature search found no references directly addressing this question. Obviously, some threshold of muscle contraction exists which probably reduces the effective compliance of vessels in the tissue: everyone knows that an isometrically contracted muscle feels stiffer (less compliant) than when relaxed. Quantification of this potential effect on vessel compliance is needed.

Therefore, this report presents fundamental and original findings, and also provides interesting and potentially fruitful directions for future work.

## **Appendix A – System for Ambulatory Measurement of Central Venous Pressure**

For the confirmation of Katkov and Chestukhin's 1980 upper body venous pressure data (see sec. 3), CVP was measured directly in the superior vena cava to  $\pm 0.1$  mmHg using an SMCVP (Buckey et al., 1987; Buckey et al., 1991). This system was designed to safely, accurately, and reliably measure CVP under the rigorous "field" conditions of space flight (Space Life Science I and II series of Shuttle Spacelab flight experiments, E-294, Cardiovascular Adaptation to Microgravity; PI: C. G. Blomqvist). Section 3 gives details of the catheterization and experimental procedures. This appendix summarizes a report by Buckey and colleagues (1991) describing the development and features of the SMCVP.

The battery-operated unit consists of a transducer to measure pressure, a pump to infuse heparinized saline through the catheter to keep it patent, and an electronics package to run the pump and mediate the signal from the transducer. The transducer is an Endevco model 8510B-2. It was chosen for its low drift characteristics and high temperature stability. The transducer is housed in a small flat plastic block which is taped in place under the subject's arm based on fluoroscopic imaging of the catheter and right atrium. A wire cable and saline-filled tube connect the transducer to the electronics package and pump housing, respectively. The electronics package and pump are contained in the same housing, which fits in a

pocket over the thigh or in a fanny pack. To ensure isolation of the subject from any current leakage, the transducer is isolated from the saline column by two latex diaphragms surrounding a chamber in the transducer block filled with Dow Corning 360 medical fluid, which is nonconductive. The pump slowly (1.5 ml per hour) infuses heparinized saline (30 units heparin per ml) into the catheter to prevent clotting. The saline-filled pump chamber also completes the fluid connection between the catheter tip and the pressure transducer. The units were calibrated manually with a fluid column before and after each use. SMCVP units are assembled under sterile conditions, and components are disassembled and autoclaved between uses. The SMCVP provides a 0–5 volt analog signal and digital liquid crystal display to measure pressures between  $-3$  and 25 mmHg.

Using the SLS investigator team as subjects, we have tested the SMCVP in a variety of conditions, including daily activities, centrifugation (Buckey et al., 1986), parabolic flight microgravity, and multiple emergency egress simulations, including a drop of the subject from height into water (Buckey et al., 1991). Importantly, the SMCVP has performed well and collected provocative data during launch of the Shuttle and the first several hours in orbit in a total of three crewmembers on two different space flights (Buckey et al., 1993; Buckey et al., in press). The instrument is more than suitable for collecting data to compare to results of Katkov and Chestukhin (1980; sec. 3).

## Appendix B – System For Venous Occlusion Plethysmography

A new and unique limb plethysmograph was used to collect about half of the supine venous occlusion calf venous compliance data reported in section 5. This device, called the SVOP (system for venous occlusion plethysmography), was developed to measure calf blood flow and venous compliance in microgravity for the Space Life Science I and II series of Shuttle Spacelab flight experiments (E-294, Cardiovascular Adaptation to Microgravity; PI: C. G. Blomqvist). This appendix summarizes findings reported by Buckey and colleagues (1985) describing our comparisons of the SVOP to conventional mercury-in-silastic strain gauge plethysmography (Whitney, 1953). The SVOP operates on similar principles to liquid metal-in-silastic strain gauge plethysmography, in that it measures changes in limb circumference which allow calculation of changes in limb volume. However, the SVOP contains no toxic materials such as mercury. In addition, it produces a constant voltage output per mm limb circumference change, and thus requires no calibration. The need for safety and ease of use in the Spacelab microgravity environment drove development of these features.

The SVOP essentially consists of an optical shaft encoder connected to a 2.5 cm wide Mylar band around the limb, with an electronics package which converts the shaft encoder output into an analog voltage signal. The Mylar band-skin interface is lubricated with an aqueous gel (commonly used for ultrasound transmission) to ensure that limb expansion is accurately transmitted to the shaft encoder. As the limb expands during venous occlusion, the Mylar band pulls on and rotates the shaft encoder in direct and precalibrated proportion to the amount of limb circumference elevation. Thus the voltage output of the SVOP unit directly reflects the degree of limb circumference elevation, and limb volume elevation may then be calculated according to the geometric relationships between circumference and volume (sec. 2). SVOP sensitivity equals  $\pm 0.02$  mm, which rivals sensitivity of liquid metal-in-silastic strain gauge systems.

We compared SVOP measurements of resting and hyperemic calf blood flow to those made with conventional mercury-in-silastic strain gauge plethysmography in five healthy supine subjects. Both legs were elevated about  $15^\circ$  from horizontal on foam cushions, with the knees comfortably bent; 60 mmHg thigh venous occlusion was employed. Calf blood flow measurements were made at rest and during the hyperemia following 3 min of thigh arterial occlusion at 250 mmHg. Resting and hyperemic measurements were made simultaneously with both instruments, with the strain gauge on one leg and the SVOP on the other. Measurements were repeated after switching the devices to the alternate leg. A total of 111 paired measurements were made. Linear regression related SVOP and strain gauge calf flow measurements.

SVOP and conventional strain gauge leg blood flow measurements agreed well: the equation relating the two was  $SVOP = 0.90(Whitney) + 0.44$ . The slope of this relationship did not differ significantly from identity (1), and the intercept did not differ from zero. The relationship between the two measurement systems exhibited an  $r^2$  of 0.90. Resting and hyperemic flow calf blood flow measurements encompass the same range of use of the SVOP as the venous compliance measurements reported in section 5. Therefore, the SVOP provides comparable measurements of venous occlusion-induced calf volume elevation to those provided by conventional mercury-in-silastic strain gauge plethysmography. The SVOP does underestimate *reduction* of calf volume following release of venous occlusion cuff pressure. This deficiency requires “re-snugging” of the Mylar band against the leg surface after calf volume has returned to baseline levels (Buckey et al., 1985). If such re-snugging is not performed, then the Mylar band will not be properly seated against the gel-skin surface prior to the next venous occlusion-induced expansion of the leg, and subsequent leg expansion will be underestimated. Nevertheless, when used properly, the SVOP generates data comparable to those produced by conventional mercury-in-silastic strain gauge systems. Therefore, data from the SVOP are appropriate for inclusion in section 5.

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13. ABSTRACT (Maximum 200 words) Human venous compliance hypothetically decreases from upper to lower body as a mechanism for maintenance of the hydrostatic indifference level "headward" in the body, near the heart. This maintains cardiac filling pressure, and thus cardiac output and cerebral perfusion, during orthostasis. This project entailed four steps. First, acute whole-body tilting was employed to alter human calf and neck venous volumes. Subjects were tilted on a tilt table equipped with a footplate as follows: 90°, 53°, 30°, 12°, 0°, -6°, -12°, -6°, 0°, 12°, 30°, 53°, and 90°. Tilt angles were held for 30 sec each, with 10 sec transitions between angles. Neck volume increased and calf volume decreased during head-down tilting, and the opposite occurred during head-up tilt. Second, I sought to cross-validate Katkov and Chestukhin's (1980) measurements of human leg and neck venous pressures during whole-body tilting, so that those data could be used with volume data from the present study to calculate calf and neck venous compliance (compliance = $\Delta\text{volume}/\Delta\text{pressure}$ ). Direct measurements of venous pressures during postural changes and whole-body tilting confirmed that the local changes in venous pressures seen by Katkov and Chestukhin (1980) are valid. The present data also confirmed that gravitational changes in calf venous pressure substantially exceed those changes in upper body venous pressure. Third, the volume and pressure data above were used to find that human neck venous compliance exceeds calf venous compliance by a factor of 6, thereby upholding the primary hypothesis. Also, calf and neck venous compliance correlated significantly with each other ( $r^2 = 0.56$ ). Fourth, I wished to determine whether human calf muscle activation during head-up tilt reduces calf venous compliance. Findings from tilting and from supine assessments of relaxed calf venous compliance were similar, indicating that tilt-induced muscle activation is relatively unimportant. Low calf venous compliance probably results from stiffer venous, skeletal muscle, and connective tissues, and better-developed local and central neural controls of venous distensibility. This research establishes that upper-to-lower body reduction of venous compliance can explain headward positioning of the hydrostatic indifference level in humans.				
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